

EXHIBIT

1

**EXPERT REPORT
DAVID KESSLER, M.D.**

PART A: QUALIFICATIONS AND SCOPE	10
I. QUALIFICATIONS	10
II. SCOPE	13
PART B: STANDARDS.....	14
III. RESPONSIBILITIES UNDER THE FOOD DRUG AND COSMETICS ACT.....	14
A. Information About a Drug Must Be Truthful.....	15
B. The Risks and Benefits of a Drug Must Be Presented in a Balanced Fashion	17
C. Promotional Statements Need to Be Supported by Substantial Evidence.....	17
D. New Safety Information Must Be Conveyed Upon Receipt to Inform Healthcare Providers and Patients About New Safety Risks.....	18
E. Drug Manufacturers Cannot, Under the Guise of Sponsoring Medical Education, Convey Misleading Promotion	19
F. Promotional Information Needs to Be Evaluated by the Totality of the Impression it Creates	20
G. Drug Manufacturers May Not Promote Unapproved or Off-Label Uses	21
H. Promotional Activities Are Recognized to Influence the Prescriber.....	21
I. Drug Manufacturers Have a Responsibility to Engage in the Dissemination of Information in Order to Minimize Risks.....	22
J. The Manufacturer of a Drug Has Primary Responsibility for a Drug’s Safety and its Promotional Information	24
K. Deviations from or Non-Conformance with FDA Requirements on Marketing and Promotion Puts Consumers at Risk	25
L. Corrective Marketing May Be Used to Counteract Misleading Information About a Drug’s Risks and Benefits.....	25
PART C: THE OPIOID MANUFACTURERS’ MARKETING AND PROMOTION DEVIATED FROM FDA STANDARDS, INCREASING THE RISK OF ABUSE AND ENDANGERING PATIENT SAFETY ..	28
IV. PRIOR TO THE INTRODUCTION OF OXYCONTIN, HEALTHCARE PROVIDERS EXERCISED CAUTION IN PRESCRIBING STRONG OPIOIDS .	28
V. PURDUE.....	31
A. Overview	31
B. Purdue’s Marketing Strategy for OxyContin	34

C.	Purdue Promoted OxyContin in a Manner that Understated its Risks, Overstated its Benefits, and for Indications that Lacked Substantial Evidence to Support Safety and Efficacy.....	39
1.	Purdue’s Promotion of OxyContin and Opioids in General Minimized the Risks of Abuse, Addiction, Tolerance, and the Effects of Withdrawal.....	40
(a)	Purdue’s Marketing Misleadingly Minimized the Similarities Between OxyContin and Morphine.	40
(b)	Purdue Falsely Marketed OxyContin as Having a Lower Potential for Abuse as Compared to Other Opioid Products ...	46
(c)	Purdue Lacked Substantial Evidence Regarding the Addictive Potential of OxyContin, Yet Misleadingly Claimed that OxyContin Was Less Addictive than Competitor Opioid Products.	56
(d)	Purdue Misleadingly Told Health Care Providers that Patients Exhibiting Signs of Addiction Were Likely “Pseudoaddicted” and in Need of Additional Opioids to Treat Pain	62
(e)	Purdue Minimized the Risks of Tolerance and Physical Dependence that Patients Could Experience with OxyContin	67
(f)	Purdue’s Marketing Minimized the Risks of Respiratory Depression, Addiction, and Abuse Associated with Higher Doses of OxyContin	73
2.	In Response to OxyContin Not Being Effective for 12 Hours, Purdue Developed a Strategy to Increase the Total Daily OxyContin Dose but Failed to Inform the Public, Putting Patients at Risk.	80
3.	Purdue Overstated the Benefits of OxyContin with Respect to Sleep, Work, and Physical Activity and Leisure.....	88
4.	Purdue Promoted OxyContin for Indications that Were Broader than Supported by Substantial Evidence and for Which Safety and Efficacy Were Not Established	94
D.	Despite Ongoing and Increasing Evidence of OxyContin Abuse, Purdue Failed to Take Reasonable Steps to Correct its Prior Misleading Statements Regarding the Safety of OxyContin and Opioids in General	101
1.	Purdue’s Promotion and Sales of OxyContin Increased as Reports of Abuse Grew.....	101

2.	FDA Advised Purdue that it Needed to Correct Misinformation Regarding Opioids through a Risk Management Plan and Limit the Expanded Use of Opioids	103
3.	Despite FDA’s Warnings Regarding the Impact of Misinformation Concerning Opioids, Purdue Failed to Take Reasonable Steps to Correct its Misleading Statements and Continued to Expand the Opioid Market	105
VI.	ENDO.....	109
A.	Overview	109
B.	Percocet	110
1.	Endo’s Marketing Strategy for Percocet	110
2.	FDA Approval of Additional Percocet Tablet Strengths	111
3.	Endo Funded Promotional Activities for Percocet; Those Activities Understated the Risks of the Entire Class of Opioids	111
(a)	Endo Funded Promotional Activities to Market Percocet	111
(b)	Endo’s Brand Marketing of Percocet Minimized the Risks of Respiratory Depression and Abuse Associated With Higher Doses of Opioids	118
(c)	Endo Overstated the Benefits of Percocet With Respect to Quality of Life	120
4.	As Reports of Percocet Abuse Grew, Endo’s Promotion and Sales of Percocet Increased	121
C.	Opana ER.....	122
1.	Endo’s Marketing Strategy for Opana ER.....	124
2.	Endo Promoted Opana ER in a Manner that Understated Its Risks and Overstated Its Benefits.....	129
(a)	Endo Falsely Marketed Opana ER as Having a Lower Abuse Potential and as Safer than Other Opioid Products.....	129
(b)	Endo Minimized the Risk of Addiction Associated with Opana ER and Funded Various Pain Organizations to Likewise Minimize the Risk of Addiction.....	134
(c)	Endo Falsely Told Healthcare Providers that Patients Exhibiting Signs of Addiction Could be Exhibiting “Pseudoaddiction” and in Need of Additional Opioids to Treat Pain	136

(d)	Endo’s Promotion of Opana ER Minimized the Risks of Respiratory Depression, Addiction and Abuse Associated With Higher Doses	139
(e)	Endo Overstated the Benefits of Opana ER With Respect to Work and Functionality	140
3.	Endo’s Risk Minimization Action Plan for Opana ER Contained Elements that Understated the Risk Abuse and Addiction and Misleadingly Claimed that Patients Exhibiting Signs of Addiction Were Likely “Pseudoaddicted”	141
(a)	Elements of the “Professional Education Initiatives” in the Opana ER RiskMap Falsely Told Healthcare Providers that Patients Exhibiting Signs of Addiction Could Be Exhibiting “Pseudoaddiction” and in Need of Additional Opioids to Treat Pain	144
(b)	Elements of the “Professional Education Initiatives” in the Opana ER RiskMap Minimized the Risk of Addiction Associated with Opioids.....	147
4.	Endo’s Promotion and Sales of Opana ER Increased as Reports of Abuse Grew.....	149
D.	Opana ER Reformulated	156
1.	Endo’s Marketing Strategy for Opana ER Reformulated	156
2.	FDA Denial of Abuse Deterrent Claim as to Opana ER Reformulated	156
3.	Endo Marketed Opana ER Reformulated as “Crush Resistant” Despite FDA’s Instruction Otherwise.....	158
4.	Despite Increasing Evidence of Abuse of Opana ER Reformulated, Endo Continued to Promote Opana ER Reformulated in the Manner Described Above and Thus Put the Public Health At Risk.....	161
VII.	JANSSEN.....	163
A.	Overview	163
B.	Duragesic	164
1.	Regulatory Background	164
(a)	Relevant labeling history.....	164
(b)	Pre-Approval FDA Correspondence	166

2.	Janssen's Marketing of Duragesic Broadened its Indications, Expanding the Use of Long Acting Opioids and Contributing to the Change in the Practice of Medicine.....	168
(a)	Janssen's Marketing Focus Shifted from Cancer Pain to Non-Cancer Chronic Pain in the Mid-1990s.....	168
(b)	Janssen's Marketing Misrepresented Duragesic's Efficacy and Risks for Chronic Non-Cancer Pain.....	173
3.	Janssen's Promotion of Duragesic Understated its Risk and Overstated its Benefits.....	180
(a)	Janssen Promoted Duragesic as Superior to Oral Opioids, Especially OxyContin, Without Substantial Evidence.	180
(b)	DDMAC Warned Janssen That its Functionality Claims and Superiority Claims Comparing Duragesic to Oral Opioids Were Misleading.	185
4.	Janssen Promoted Duragesic as Having No or Lower Abuse Potential, Particularly Compared with OxyContin, Without Substantial Evidence.	193
5.	Janssen Made Shifting and Unsubstantiated Claims Regarding the Abuse Potential of the Reservoir v. Matrix Formulations of Duragesic as the Sales Environment for the Drug Shifted.	200
C.	Nucynta.....	214
1.	Janssen's Marketing Strategy for Nucynta.....	215
(a)	Covering Acute to Chronic Continuum	215
(b)	Disrupting the Complacent Market.....	218
(c)	Pre-Market FDA Statements Regarding the Safety and Efficacy of Nucynta IR	219
(d)	Pre-Market FDA Statements Regarding the Safety and Efficacy of Nucynta ER	222
2.	Janssen's Marketing of Nucynta Overstated its Benefits.....	225
(a)	Janssen Overstated the Benefits of Nucynta's Mechanism of Action	226
(b)	Janssen Overstated the Benefits of Nucynta's GI Tolerability	234

3.	Janssen’s Promotion of Nucynta Minimized the Risks of Abuse and Withdrawal During an Opioid Abuse Epidemic.	241
VIII.	TEVA	252
A.	Overview	252
B.	Actiq	253
1.	Approval of Actiq for Limited Use.	253
2.	Teva Marketed Actiq for Non-Malignant Pain, for Which Safety Had Not Been Established by Substantial Evidence.....	254
3.	Teva Failed to Comply with its Risk Management Strategies in Marketing Actiq	258
C.	Fentora	260
1.	Approval of Fentora for Limited Use.	260
2.	Teva Promoted Fentora for Non-Malignant Pain, for which it Lacked Substantial Evidence to Support Safety	261
IX.	ACTAVIS	263
A.	Overview	263
B.	Actavis Promoted Kadian in a Manner that Understated Its Risks, Overstated Its Benefits, and for Indications that Lacked Substantial Evidence to Support Safety and Efficacy.....	263
1.	Actavis Promoted Kadian for Indications Broader than Supported by Substantial Evidence and for Which Safety and Efficacy Were Not Established.	264
2.	Actavis Overstated the Benefits of Kadian with Respect to Functionality and Quality of Life.	266
(a)	Actavis Falsely Marketed Kadian as Safer and More Effective than Other Opioid Products.....	267
(b)	Actavis Misleadingly Promoted Kadian as Having No Alcohol-Induced Dose Dumping Effect.....	271
3.	Actavis’s Promotion of Opioids Minimized the Risks of Addiction and Abuse.	275
X.	MALLINCKRODT	276
A.	Overview	276

B.	Exalgo	277
1.	Mallinckrodt’s Marketing Strategy for Exalgo	277
2.	Mallinckrodt Promoted Exalgo in a Manner that Understated its Risks and Overstated its Benefits	278
(a)	Mallinckrodt Falsely Promoted Exalgo as Safer than other Opioid Products	278
(b)	Mallinckrodt’s sales training misleadingly minimized the risks associated with higher doses of opioids and encouraged sales representatives to make misleading claims regarding abuse deterrence	283
(c)	Mallinckrodt Misleadingly Minimized the Risk of Addiction and Funded the CARES Alliance, Which Likewise Understated the Risk of Addiction	285
(d)	Mallinckrodt Misleadingly Told Health Care Providers that Patients Exhibiting Signs of Addiction Were Likely “Pseudoaddicted” and in Need of Additional Opioids to Treat Pain	286
C.	Xartemis XR	289
1.	Mallinckrodt’s Marketing Strategy for Xartemis	289
2.	Mallinckrodt Misleadingly Marketed Xartemis as Having a Lower Potential for Abuse as Compared to Other Opioid Products.	291
XI.	THE OPIOID MANUFACTURERS’ SUPPORT FOR AND INVOLVEMENT WITH PAIN ADVOCACY, PROFESSIONAL MEDICAL AND TRADE GROUP ORGANIZATIONS, EXPANDED THE USE OF OPIOIDS AND INCREASED THE RISK OF ABUSE	295
A.	American Pain Society	296
1.	APS/AAPM Guideline – The Use of Opioids for the Treatment of Chronic Pain.....	298
2.	APS/AAPM/ASAM – Definitions Related to the Use of Opioids for the Treatment of Pain.....	300
3.	APS Arthritis Guidelines	301
B.	American Academy of Pain Medicine	303
C.	American Pain Foundation.....	305
D.	Federation of State Medical Boards	309

1.	FSMB Model Guidelines for the Use of Controlled Substances for the Treatment of Pain.....	311
2.	Updated FSMB Policy for the Use of Controlled Substances for the Treatment of Pain.....	311
3.	FSMB Responsible Opioid Prescribing.....	313
XII.	CORRECTIVE MEASURES	314
XIII.	CONCLUSIONS.....	315

PART A: QUALIFICATIONS AND SCOPE

I. QUALIFICATIONS

1. My name is David A. Kessler, M.D. I received my M.D. degree from Harvard Medical School in 1979 and my J.D. degree from the University of Chicago Law School in 1978.

2. I did my pediatrics training at Johns Hopkins Hospital.

3. I was appointed in 1990 by President George H. W. Bush as Commissioner of the United States Food and Drug Administration (“FDA”) and was confirmed by the United States Senate. I also served in that position under President William Jefferson Clinton until February 1997.

4. I have taught food and drug law at Columbia University Law School, and I have testified many times before the United States Congress on food, drug, and consumer protection issues under federal and state law. Over the last thirty years, I have published numerous articles in legal, medical, and scientific journals on the federal regulation of food, drugs, and medical devices. I have had special training in pharmacoepidemiology at Johns Hopkins Hospital. My resume, including a list of my published books and articles, is included in Appendix A. A list of cases in which I have appeared as a witness, and documentation of my expert witness fee, is attached as Appendix B.

5. As Commissioner, I had ultimate responsibility for implementing and enforcing the United States Food, Drug, and Cosmetic Act. I was responsible for overseeing five Centers within the FDA. They included, among others, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health and the Center for Biologics Evaluation and Research. In addition to those duties, I placed high priority on getting promising therapies for serious and life-threatening diseases to patients as quickly as possible. During my tenure as Commissioner, the FDA announced a number of new programs including: the regulation of the

marketing and sale of tobacco products to children; nutrition labeling for food; user fees for drugs and biologics; preventive controls to improve food safety; measures to strengthen the nation's blood supply; and the MEDWatch program for reporting adverse events and product problems involving both drugs and devices. I created an Office of Criminal Investigation within the Agency to investigate suspected criminal violations of the Food, Drug, and Cosmetic Act, FDA regulations, and other related laws. I worked closely with and was ultimately responsible for the FDA's Division of Drug Marketing, Advertising and Communications. I have published articles on drug promotion and marketing practices.¹ I have likewise written extensively on the issue of addiction and have been heavily involved in the science of addiction since investigating and regulating nicotine-containing tobacco products while at FDA.

6. I am a senior advisor to TPG Capital, a leading global private equity firm, which owns pharmaceutical and biomedical companies. I previously served on the board of Aptalis Pharma and Tokai Pharmaceuticals, and I currently serve on the board of the medical device and biologics company Immucor, Inc. In these advisory and fiduciary capacities, I have advised companies on the standards and duties of care in the pharmaceutical and medical device industry. I also previously chaired the compliance committees of Aptalis, and I currently chair the quality committee of Immucor, which involves ensuring compliance with FDA laws and requirements.

7. Listed in Appendix C are documents I accessed independently from various sources, including but not limited to the FDA's website and the relevant discovery databases, and documents that have been provided to me by counsel. At my request, Appendix C was prepared

¹ These include: Kessler, D. (1990). The federal regulation of prescription drug advertising and promotion. JAMA 264:2409-15); Kessler, D. (1991). Drug promotion and scientific exchange. The role of the clinical investigator. N Engl J Med 325:201-3; Kessler, D. (1991). Communicating with patients about their medications. N Engl J Med 325:1650-2; Kessler, D. Therapeutic-class wars--drug promotion in a competitive marketplace. N Engl J Med 331:1350-3; Kessler, D. (2007). Direct-to-consumer advertising: is it too late to manage the risks? Ann Fam Med 5:4-5.

by counsel. Based on my review of those documents and my training and experience, I have a number of opinions that are detailed below.

8. The causes of action in this litigation include: public nuisance; negligence; common law fraud; civil conspiracy; violation of the Racketeer Influenced and Corrupt Organizations (“RICO”) Act; violation of consumer protection laws; and unjust enrichment.

9. It is my understanding that the plaintiffs include: County of Cuyahoga and County of Summit.

10. Likewise, it is my understanding that the defendants in this action are as follows: Actavis LLC, Actavis Pharma, Inc., Allergan Finance LLC, Allergan PLC, AmerisourceBergen Drug Corporation, ANDA, Inc., Cardinal Health, Inc., Cephalon, Inc., CVS Indiana, LLC, CVS Rx Services, Inc., Discount Drug Mart, Inc., Endo Health Solutions Inc., Endo Pharmaceuticals, Inc., H.D. Smith Holding Company, H.D. Smith Holding Company (County of Cuyahoga Only), H.D. Smith Holdings LLC, H.D. Smith Holdings, LLC (County of Cuyahoga Only), H.D. Smith LLC d/b/a H.D. Smith, H.D. Smith, LLC d/b/a H.D. Smith (County Of Cuyahoga Only), HBC Service Company, Health Mart Systems, Inc., Health Mart Systems, Inc. (County of Cuyahoga only), Henry Schein Medical Systems, Inc., Henry Schein Medical Systems, Inc. (County of Summit only), Henry Schein, Inc., Henry Schein, Inc. (County of Summit only), Insys Therapeutics, Inc., Janssen Pharmaceuticals, Inc., Johnson & Johnson, Mallinckrodt LLC, Mallinckrodt PLC, McKesson Corporation, Miami-Luken, Inc., Noramco, Inc., Par Pharmaceutical Companies, Inc., Par Pharmaceutical, Inc., Prescription Supply, Inc., Purdue Pharma, Inc., Purdue Pharma, L.P., Rite Aid of Maryland, Inc. d/b/a Rite-Aid Mid-Atlantic Customer Support Center, Inc., Specgx LLC, Teva Pharmaceutical Industries, Ltd., Teva

Pharmaceuticals USA, Inc., The Purdue Frederick Company, Inc., Walgreen Co., Walgreen Eastern Co., Walmart Inc., Watson Laboratories, Inc.

11. The opioid products discussed in this report include: OxyContin (Purdue), OxyContin Reformulated (Purdue), MS Contin (Purdue), Opana ER (Endo), Opana ER reformulated (Endo), Percocet (Endo), Duragesic (Janssen), Nucynta IR (Janssen), Nucynta ER (Janssen), Actiq (Teva), Fentora (Teva), Kadian (Actavis), Exalgo (Mallinckrodt), Xartemis ER (Mallinckrodt), and generic OxyContin (Mallinckrodt).

II. SCOPE

12. I have been asked by counsel for the plaintiffs to discuss drug sponsor obligations under standards provided under United States food and drug laws, regulations, guidances, and industry practice as they pertain to prescription opioids, and to discuss the purposes of those obligations and standards and the effect, if any, that any departures from those standards would be expected to have on the use, misuse and abuse of prescription opioids during the past two decades or so. I have also been asked to review the discovery records of specified defendant opioid manufacturers² for the purpose of formulating an opinion as to whether any one or more of those manufacturers departed from accepted drug regulatory standards and, if so, to describe how.³

² As used throughout this report, the term "manufacturer" refers to a sponsor of a drug.

³ The following Schedules are attached to this Report:

Schedule 1 contains general information about the drugs that are the subject of this Report.

Schedule 2 contains the approval dates of various dosages of the drugs that are the subject of this Report.

Schedule 3 contains a Morphine Milligram Equivalent (MME) conversion table.

Schedule 4 contains definitions of addiction and related terms.

Schedule 5 contains a list of Defendants and Plaintiffs in this MDL.

Schedule 6 contains relevant communications from FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC).

Schedule 7 contains relevant FDA Advisory Committee materials.

Schedule 8 contains IMS sales data for the drugs that are the subject of this Report. I understand from counsel that this Schedule has been prepared by Greylock McKinnon Associates.

Schedule 9 contains FDA's Risk Evaluation and Mitigation Strategies (REMS) requirements for oral opioids.

PART B: STANDARDS

III. RESPONSIBILITIES UNDER THE FOOD DRUG AND COSMETICS ACT

13. FDA is a public health, consumer protection agency. The agency regulates not only the approval of prescription drugs but also their marketing and promotion. The principles in FDA's regulation of marketing and promotion help (1) assure that consumers can make informed choices with their doctors about the use of medicines by being able to weigh the risks and benefits; (2) prevent the exposure of patients to potentially serious and avoidable health risks; (3) assure that medicines are used safely; and (4) prevent the inappropriate prescription (e.g., incorrect treatment choice, over or under prescription of the drug, etc.).

14. According to the Food Drug and Cosmetic Act ("FDCA" or "the Act"), FDA has jurisdiction over prescription drug labeling.

15. The Act defines label to mean "a display of written, printed, or graphic matter upon the immediate container of any article ..." ⁴ According to FDA regulations, "Label means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity." ⁵ The Act defines labeling to mean "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." ⁶ Similarly, FDA regulations provide that labeling includes "all

Schedule 10 contains FDA's REMS requirements for Transmucosal Immediate Release Fentanyl.
Schedule 11 contains relevant sales representative call notes for drugs that are the subject of this Report.
Schedule 12 contains chronologies of relevant changes to the labels of the drugs that are the subject of this Report.
All Schedules other than Schedule 8 were prepared by legal staff under my direction and subject to my review.

⁴ 21 U.S.C. § 321(k) (2016).

⁵ 21 CFR § 1.3(b) (2018).

⁶ 21 U.S.C. 321(m) (2016).

written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.”⁷

16. FDA generally describes labeling as comprising two types: (1) the label and (2) promotional labeling.

17. Promotional labeling includes statements and materials issued by, on behalf of, or with the involvement of a drug sponsor or manufacturer.

18. Promotional labeling shapes what healthcare providers and consumers understand about a drug—its safety, efficacy, and how to use it.

19. The key principles in FDA’s regulation of marketing and promotion include the following:

A. Information About a Drug Must Be Truthful

20. Promotional labeling must not be false or misleading. Under FDA regulations, certain types of statements are considered to be “false or misleading,” such as:

- “Contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, useful in a broader range of conditions or patients ..., safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience...”⁸
- “Contains a drug comparison that represents or suggests that a drug is safer or more effective than another drug in some particular when it has not been demonstrated to be safer or more effective in such particular by substantial

⁷ 21 CFR § 1.3(a) (2018).

⁸ 21 CFR § 202.1(e)(i) (2018). The FDA has applied this standard to quality of life and patient preference claims as well. *See, e.g.*, DDMAC Letter to GlaxoSmithKline re FLONASE, May 9, 2007.

evidence or substantial clinical experience.”⁹

- “Contains a representation or suggestion that a drug is safer than it has been demonstrated to be by substantial evidence or substantial clinical experience, by selective presentation of information from published articles or other references that report no side effects or minimal side effects with the drug or otherwise selects information from any source in a way that makes a drug appear to be safer than has been demonstrated.”¹⁰

21. The Act states that whether a drug’s labeling or advertising is misleading should take into account “not only representations made or suggested” but also “the extent to which the labeling or advertising fails to reveal facts material in light of such representation.”¹¹

22. The importance of truthful and non-misleading information in promotional materials is underscored by FDA stating:

FDA believes it is critically important to disclose risk information in prescription drug and medical device promotion appropriately and effectively to healthcare professionals and consumers. This information helps consumers know whether drugs or devices may be appropriate for them as well as what they should tell their healthcare professionals about before taking or using or while taking or using a product. It also lets consumers know what risks they might experience and what steps they need to take for safety reasons (e.g., no driving) because of taking or using a product. Appropriate risk disclosures help healthcare professionals by giving them some of the information they need to know about the product that will enable them to safely use or prescribe it.¹²

⁹ 21 CFR § 202.1(e)(ii) (2018).

¹⁰ 21 CFR § 202.1(e) (iv) (2018).

¹¹ 21 U.S.C. § 321(n) (2016).

¹² FDA, Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion at 5-6 (May 2009).

B. The Risks and Benefits of a Drug Must Be Presented in a Balanced Fashion

23. With respect to promotional materials, manufacturers must “present a fair balance between information relating to the side effects and contraindications and information relating to the effectiveness of the drug.” FDA explains fair balance as follows: “The law requires that product claim ads give a ‘fair balance’ of information about drug risks as compared with information about drug benefits. This means that the content and presentation of a drug’s most important risks must be reasonably similar to the content and presentation of its benefits.”¹³

24. In a draft guidance, FDA stated,

Although the regulations [regarding fair balance, disclosure of risks, and similar matters] were promulgated in the context of prescription drug advertising, the guidance they provide on what FDA considers false or misleading in promotion has broader applicability. For example, promotional pieces that fail to present a balanced view of the risks and benefits of a product are generally considered to be false or misleading and also generally fail to reveal material facts about the product being promoted. Because both labeling pieces for drugs and devices, and advertising pieces for prescription drugs and restricted devices, are considered to misbrand a product if they are false or misleading or fail to reveal material facts, drug and device manufacturers should take into account the guidance provided by these regulations when promoting a drug.¹⁴

C. Promotional Statements Need to Be Supported by Substantial Evidence

25. Under United States food and drug laws, a drug may not be introduced into interstate commerce unless its sponsor has shown that the drug is safe and effective for the intended conditions of use as established by substantial evidence.¹⁵

26. Likewise, all product claims must be supported by substantial evidence.¹⁶

¹³ <https://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htm#F>

¹⁴ FDA, Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion at 12 (May 2009).

¹⁵ 21 U.S.C. § 321 (2016).

¹⁶ 21 C.F.R. § 201.1(e)(4)(ii)(b) and (c) (2018).

27. The law requires that “adequate and well-controlled investigation” be used to demonstrate a drug’s safety and effectiveness,¹⁷ and the FDA has typically required that substantial evidence consist of at least two adequate and well-controlled clinical trials.¹⁸

D. New Safety Information Must Be Conveyed Upon Receipt to Inform Healthcare Providers and Patients About New Safety Risks

28. Generally, a drug manufacturer has responsibility to update the label and labeling upon receipt of evidence that suggests a reasonable possibility of a causal association between a drug and an adverse event.

29. Procedural mechanisms exist under FDA regulations whereby a drug manufacturer can make changes to the label and labeling called “Changes Being Effected.”¹⁹

30. As FDA stated in 1979, nothing in the Act prohibits a manufacturer from warning healthcare providers and consumers about important safety risks.²⁰

31. The approval of a drug at one point in time does not relieve a drug manufacturer from the responsibility to update and convey important safety information to healthcare providers and patients.

¹⁷ 21 U.S.C. § 355(d) (2018).

¹⁸ FDA, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic Products at 4 (May 1998).

¹⁹ See 21 CFR 314.70; FDA, *Guidance for Industry: Changes to an Approved NDA or ANDA* (April 2004). Pharmaceutical drug manufacturers must make reports to the FDA, including Annual Reports that provide a “Summary” section that includes “A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product.” 21 C.F.R. 314.81(b)(2)(i). The Summary section “is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information” *Id.* Holders of abbreviated applications must also make such Annual Reports for each of its approved abbreviated applications. 21 C.F.R. 314.81(b); see, e.g., 3/25/29 Dep. of Scott Tomsy, and Exhs. 7, 11 and 13 (FDA generic opioid ANDA approvals referencing sections 314.80, 314.81 and 314.98).

²⁰ 44 Fed. Reg. 37434, 37447 (1979). Drug manufacturers may communicate safety information contained in the label through, for example, a “Dear Doctor” letter or other communication. 21 C.F.R. 201.100(d)(1).

32. The Act prohibits the delivery for introduction, and causing the delivery for introduction, into interstate commerce of a misbranded drug.²¹ A person who misbrands a drug with the intent to defraud or mislead is guilty of a felony offense.²²

E. Drug Manufacturers Cannot, Under the Guise of Sponsoring Medical Education, Convey Misleading Promotion

33. As I have written previously, the type of medical education activities that a drug manufacturer may engage in depends on whether such activities are considered “educational” or “promotional.” FDA’s drug regulations draw a critical distinction between “scientific exchange” and “promotional activities.” While the promoting or advertising of investigational drugs is prohibited, the Agency recognizes that educational exchanges among scientists regarding drugs prior to approval has scientific value. When a pharmaceutical firm supports these educational activities, however, the line between “education” and “promotion” becomes harder to draw. The distinction is obviously important to pharmaceutical firms because FDA regulates promotional activities under its prescription drug labeling and advertising regulations. Although educational activities sponsored by the manufacturer may be considered by FDA as labeling, FDA has generally exercised its discretion not to enforce that authority with respect to purely educational activities.²³

34. The criteria to distinguish educational from promotional activities include the degree to which a program is “independent” of the drug company.²⁴ “The more directly involved a company is, the more concerned FDA becomes about its promotional dimensions. Long-term

²¹ 21 U.S.C. § 331(a) (2012).

²² 21 U.S.C. § 331(a)(2) (2012).

²³ See generally Kessler DA & Pines WL. The Federal Regulation of Prescription Drug Advertising and Promotion. *JAMA* 1990; 264(18): 2409-2415.

²⁴ *Id.* at 2411.

or ongoing financial relationships between the speakers and the company will tilt the FDA's judgment toward the category of promotional activities.²⁵

35. In 1997, FDA published guidance for the industry on the proper limits of corporate sponsorship, distinguishing between "(1) Activities (programs and materials) performed by, or on behalf of, the companies that market the products; and (2) activities, supported by the companies, that are otherwise independent from the promotional influence of the supporting company."²⁶ According to FDA:

In determining whether an activity is independent of the substantive influence of a company, the agency examines whether and to what extent the company is in a position to influence the presentation of information related to its products or otherwise transform an ostensibly independent program into a promotional vehicle. FDA is concerned that companies may influence the content of educational programs both directly and indirectly. Directly, by being involved in the selection of speakers or in the treatment of topics. Indirectly, through the nature of the relationship between the company and the provider (e.g., if the provider has reason to believe that future financial support from the company depends upon producing programs that promote the company's products).²⁷

F. Promotional Information Needs to Be Evaluated by the Totality of the Impression it Creates

36. As FDA has stated in industry guidance regarding the presentation of risk information in prescription drug promotion:

It is important to emphasize that when FDA evaluates the risk communication in a promotional piece, FDA looks not just at specific risk-related statements, but at the *net impression* – i.e., the message communicated by all elements of the piece as a whole. The purpose of the evaluation is to determine whether the piece *as a whole* conveys an accurate and non-misleading impression of the benefits and risks of the promoted product. Manufacturers should therefore focus not just on individual claims or presentations, but on the promotional piece as a whole. A promotional communication that conveys a deceptive net impression of the

²⁵ *Id.*

²⁶ FDA, Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074-101 (Dec. 3, 1997).

²⁷ *Id.* at 094-096.

product could be misleading, even if specific individual claims or presentations are not misleading.²⁸

G. Drug Manufacturers May Not Promote Unapproved or Off-Label Uses

37. It is not a drug, by itself, that is regulated or that receives approval. It is a drug for an “intended use” that is reviewed and approved by FDA. Thus, it is not a chemical compound that is approved, but a chemical compound for a specific disease or condition at a specific dose that FDA reviews and approves.

38. Drugs that are promoted for uses that have not been approved by FDA have long been held to be misbranded under the Act.²⁹

39. FDA has voiced serious concerns regarding the promotion of drugs for non-approved uses. These concerns stem from the fact that the Agency has not reviewed and approved the indications for which the drug is being used.³⁰

40. Promotion of drugs for unapproved uses may put patients at risk. FDA has not reviewed or assured the safety or efficacy of the drug for unapproved uses. Moreover, promotion for unapproved uses may increase the number of patients exposed to the drug’s risks.

H. Promotional Activities Are Recognized to Influence the Prescriber

41. Disclosure of risk information in promotional materials is important because drug promotion strongly influences prescribing behavior. As noted by the World Health Organization

²⁸ FDA, Draft Guidance for Industry- Presenting Risk Information in Prescription Drug and Medical Device Promotion (May 2009) at 7.

²⁹ 21 U.S.C. § 352(f)(1) (2012).

³⁰ Testimony on Unapproved Uses of Prescription Drugs, Before the S. Comm. on Labor and Human Resources, 103rd Cong. 5 (February 22, 1996) (statement of William B. Schultz, FDA Deputy Commissioner for Policy).

in a 2002 report regarding drug promotion, “[c]ompany funding of doctors, of educational events and of research are important elements in this influence.”³¹

42. Doctors, however, typically underestimate this influence.³² As a group, we physicians like to believe that our judgment and dedication to our patients is unclouded by pharmaceutical company influences.

43. A study quoted by the World Health Organization in its 2002 report found that “reliance on information provided by the pharmaceutical industry was negatively associated with prescribing rationality. That is, doctors who relied on promotional information wrote less rational prescriptions for the case studies than those who reported relying less on promotion.”³³

I. Drug Manufacturers Have a Responsibility to Engage in the Dissemination of Information in Order to Minimize Risks

44. In 2007, the Act was amended to provide the Agency the authority to require a drug company to develop and comply with a Risk Evaluation Mitigation Strategy (REMS) for a drug for which there is a serious risk of an adverse drug experience.³⁴ REMS provide additional interventions beyond FDA-approved labeling that are necessary to ensure that the drug’s

³¹ Norris P, *Drug Promotion: what we know, what we have yet to learn*, World Health Organization and Health Action International at 73 (2005), available: http://www.who.int/medicines/areas/rational_use/drugPromodhai.pdf.

³² Reynolds E., et al. (2018). Reconciling a “pleasant exchange” with evidence of information bias: A three-country study on pharmaceutical sales visits in primary care. *Health Policy* 122:250-55.

³³ Norris P, *Drug Promotion: what we know, what we have yet to learn*, World Health Organization and Health Action International at 37 (2005), available: http://www.who.int/medicines/areas/rational_use/drugPromodhai.pdf; *see also* Alves T., et al. (2018). Medicines Information and the Regulation of the Promotion of Pharmaceuticals. *Sci Eng Ethics* doi:10.1007/s11948-018-0041-5; Fickweiler F., et al. (2017). Interactions between physicians and the pharmaceutical industry generally and sales representatives specifically and their association with physicians’ attitude and prescribing habits: a systematic review. *BMJ Open* doi:10.1136/bmjopen-2017-016408; Brax, H., et al. (2017). Association between physicians’ interaction with pharmaceutical companies and their clinical practices: a systematic review and meta-analysis. *PLoS One* 12:e0175493; DeJong, C. et al. (2016). Pharmaceutical industry-sponsored meals and physician prescribing patterns for medicare beneficiaries. *JAMA Internal Medicine* 176: 1114–1122.

³⁴ 21 U.S.C. 355-1(a)(1) (2018).

benefits outweigh its risks.³⁵ Under the Act, failure to comply with a REMS requirement renders the drug misbranded and allows for imposition of civil penalties.³⁶

45. A REMS may consist of a Medication Guide, a Patient Package Insert, or a Communication Plan,³⁷ and must include assessments and a timetable for submissions of REMS assessments.³⁸

46. FDA may also require Certain Elements to Assure Safe Use (ETASU), such as certification and/or specialized training of prescribers; certification of pharmacies or other dispensers; dispensing/administration only in certain health care settings e.g., hospitals; dispensing/administration only with evidence of safe-use conditions; requiring each patient to be subject to certain monitoring; or enrollment of treated patients in registries.³⁹

47. A responsible manufacturer whose drug requires a REMS would ensure compliance with the REMS.

48. Prior to REMS, FDA approved a small number of drugs with risk minimization action plans (RiskMaps) or required a RiskMap post-approval.⁴⁰ RiskMaps were developed for drugs, including certain opioids, that required risk management strategies beyond their FDA-approved labeling.

49. FDA's 2005 Guidance for industry, *Development and Use of Risk Minimization Actions Plans*, provided manufacturers with guidance on designing RiskMaps to minimize

³⁵ See 21 U.S.C. 355-1(a) (2018).

³⁶ See 21 U.S.C. 331(d) (2012); 21 U.S.C. 333 (2017).

³⁷ See 21 U.S.C. 355-1(e)(2)-(3) (2018).

³⁸ See 21 U.S.C. 355-1(d) (2018).

³⁹ See 21 U.S.C. 355-1(f)(3) (2018).

⁴⁰ FDA, Guidance for Industry: Development and Use of Risk Minimization Action Plans (2005) at 4-7, *available at* <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071616.pdf>

identified risks, selecting tools to minimize those risks, evaluating RiskMaps and monitoring tools, and communicating with FDA about RiskMaps.⁴¹

50. A responsible manufacturer whose drug was approved with a RiskMap must ensure that it maintains an effective RiskMap in order to minimize the risks identified in the RiskMap.

J. The Manufacturer of a Drug Has Primary Responsibility for a Drug's Safety and its Promotional Information

51. FDA regulation of a drug cannot anticipate and protect against all safety risks to individual consumers. Even the most thorough regulation of a product may fail to identify potential problems presented by the product.

52. In addition, the duties of a drug company are based not only on FDA laws and regulations, but also on the risks presented by a drug about which the company knew, should have known, or should have investigated.

53. A drug company has a responsibility, independent of what FDA directs it to do, to alert physicians and patients to risks that were unknown to or poorly understood by FDA, but were known to the company. This duty predates by decades the advent of federal regulation of drugs. *See, e.g., Thomas v. Winchester*, 6 N.Y. 397 (1852).

54. Manufacturers have superior resources that are or should be committed to overseeing the safety of the drugs they market and their promotional materials. As a result, manufacturers invariably get safety information before FDA does and have access to information that is not available to FDA. Company scientists and physicians also develop impressions and understanding of a drug's potential safety profile that may be more informed than FDA's.

⁴¹ *Id.* at 9-16.

55. Thus, what a drug company knows about a drug and what the FDA knows may be different.

K. Deviations from or Non-Conformance with FDA Requirements on Marketing and Promotion Puts Consumers at Risk

56. False or misleading promotion about drugs deprives healthcare providers and consumers of vital information that informs decision making and can thus puts consumers at risk.

57. There is a long history of FDA concerns about understatement of risks, overstatement of benefits, promotion for unproved uses, and non scientifically supported superiority claims.

58. Inappropriate marketing and promotion can result in an increase in prescribing, an inappropriate use of prescription drugs, inadequate medical care, and put consumers at increased risks.

59. When a drug has addictive properties, inappropriate marketing can result in an increase in prescribing, an inappropriate use of prescription of drugs, and an increase in the risk that the drug may be abused or cause addiction, and in increase in the risk of inadequate medical care.⁴²

L. Corrective Marketing May Be Used to Counteract Misleading Information About a Drug's Risks and Benefits.

60. As discussed above, FDA regulations require that promotion of a prescription drug contain accurate information about the drug's benefits and risks.

⁴² Hadland et al. (2019). Association of Pharmaceutical Industry Marketing of Opioid Products With Mortality From Opioid-Related Overdoses. JAMA Netw Open. 2:e186007.

61. If serious risks about a drug are not disclosed or if false or misleading information is disseminated, corrective promotion can be used to counteract these erroneous statements.⁴³

62. Research has demonstrated that corrective promotion can be effective in countering false and misleading statements made about prescription drug products.⁴⁴

63. In 2009, FDA required Bayer HealthCare Pharmaceuticals to produce and air a corrective media plan for Yaz, a birth control pill, in response to two of Bayer's advertisements for the drug that were "misleading because they broaden the drug's indication, overstate the efficacy of Yaz, and minimize serious risks associated with the use of the drug. Thus, the TV ads misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act"⁴⁵

64. FDA's letter to Bayer stated that the "violations are concerning from a public health perspective because they encourage the use of Yaz in circumstances other than those in which the drug has been approved, over-promise the benefits, and minimize the risks of Yaz."⁴⁶

⁴³ See, e.g., FDA Warning Letter to Bayer Pharmaceuticals re Yaz Tablets, Oct. 3, 2008.

⁴⁴ See <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090276.htm> ("Regarding exposure to corrective advertising, we found that a corrective ad counteracted beliefs of an overstatement of efficacy claim, but was less successful in counteracting omission of risk. Corrective ad exposure also affected perceptions of, and intended behaviors toward, the drug. Examining the effect of similarity and time delay suggests corrective ad exposure can influence consumer perceptions of drug efficacy, risks, and benefits previously established by violative ads. Corrective ads also can weaken consumer intentions to consider and seek more information about a drug. However, ad similarity does not appear to affect consumer perceptions and preferences. The length of the delay between violative and corrective ad exposure has limited influence. Broadly, these results offer evidence in support of the contention that television advertising explicitly designed to correct viewer beliefs about the risks and benefits of a prescription drug can be successful, and while further research is needed, these findings suggest that corrective advertising appears to be a viable remedy to combat some forms of misinformation through advertising.").

⁴⁵ *Id.*

⁴⁶ *Id.* FDA has sent similar letters to manufacturers when it found that their promotional materials misbranded a drug within the meaning of the FD&C Act and corrective messaging was warranted. See, e.g., FDA July 27, 2015 letter to ECR Pharmaceuticals re TussiCaps ("Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective message about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional pieces

65. To the counter the serious violations identified in FDA's warning letter, FDA requested that Bayer submit "a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional material."⁴⁷

66. In compliance with FDA's request, Bayer paid \$20 million to run a promotional campaign that told consumers that Yaz should not be taken for the inappropriate off-label uses that Bayer had promoted.⁴⁸

and/or activity, include a summary of the violate message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated."); FDA Letter to Duchesnay re Diclegis delayed-release Tablets, Aug. 7, 2015, *available at* <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM457961.pdf> ("Because the violations described above are serious and repeated, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials.")

⁴⁷ In January 2003, FDA sent a letter to Purdue requesting that it cease disseminating advertisements for OxyContin that minimized risks, overstated the efficacy of and omitted important information about the indication for OxyContin. ENDO-OPIOID_MDL-03006241 at 32. In addition, FDA requested that Purdue provide a plan of corrective action to address these promotional violations. *Id.* In response, Purdue issue a corrective advertisement, "which called attention to the warning letter and the cited violations and directed the reader to the prominently featured boxed warning and indication information for OxyContin." *Id.* "According to FDA, the corrective advertisement ran for 3 months and appeared in approximately 30 medical journals." *Id.* at n.39.

⁴⁸ See Natasha Singer, *A Birth Control Pill That Promised Too Much*, N.Y. TIMES, Feb. 8, 2009, www.nytimes.com/2009/02/11/business/11pill.html.

PART C: THE OPIOID MANUFACTURERS' MARKETING AND PROMOTION DEVIATED FROM FDA STANDARDS, INCREASING THE RISK OF ABUSE AND ENDANGERING PATIENT SAFETY

IV. PRIOR TO THE INTRODUCTION OF OXYCONTIN, HEALTHCARE PROVIDERS EXERCISED CAUTION IN PRESCRIBING STRONG OPIOIDS

67. For most of the 20th Century, American physicians approached prescribing opioids with caution,⁴⁹ believing opioids should not be used to manage chronic pain due to lack of evidence regarding their effectiveness and the risk of addiction.⁵⁰

68. The abuse of opioids in the United States is not a new phenomenon. In 1803, Friedrich Wilhelm Adam Sertürner, a German chemist, isolated a substance from crude opium.⁵¹ He named the substance morphine.⁵² The widespread use of morphine during the American Civil War resulted in wave of opioid abuse and addiction.⁵³

69. By the 1890s, medical textbooks and instructors regularly warned against overprescribing opioids,⁵⁴ and by the early 1900s the United States government sought to end the non-medicinal use of opium.⁵⁵ In 1909, Congress passed the Opium Exclusion Act, which barred the importation of opium for the purposes of smoking.⁵⁶ The Harrison Narcotics Act of

⁴⁹ Phillips JK, Ford MA, Bonnie RJ. (2017). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. National Academies Press, *available at*: <https://www.ncbi.nlm.nih.gov/books/NBK458661/Phillips>.

⁵⁰ *Id.*

⁵¹ *Id.*

⁵² *Id.*

⁵³ Erick Trickey, *Inside the Story of America's 19th-Century Opiate Addiction*, Smithsonian Mag (Jan. 4, 2018), <https://www.smithsonianmag.com/history/inside-story-americas-19th-century-opioids-addiction-180967673>.

⁵⁴ *Id.*

⁵⁵ *The History of Opiates*, Michael's House, <https://www.michaelshouse.com/opiate-rehab/history-of-opiates/> (last visited Sept. 21, 2018).

⁵⁶ *Id.*

1914 required physicians and pharmacists to register to distribute opium.⁵⁷ By 1930, heroin traffic had dropped substantially due to domestic and international restrictions,⁵⁸ and in order to avoid addiction, opioid prescribing was mainly limited to treating acute pain in the dying.⁵⁹

70. Oxycodone, a semi-synthetic opiate manufactured by modifying a chemical found in opium, was first introduced in 1916,⁶⁰ and in the next few decades was used mainly for acute pain.⁶¹ It became more widely available in the 1950s when the FDA approved Percodan, a mix of oxycodone and aspirin.⁶² The late 1970s and early 1980s brought the approval of additional immediate release opioids, including Percocet (oxycodone hydrochloride and acetaminophen) in 1976 and Vicodin (hydrocodone and acetaminophen) in 1983.⁶³

71. The dangers of oxycodone have been known for over 50 years. In 1960, the United Nations Office on Drugs and Crime classified oxycodone as a dangerous drug as part of The Dangerous Drugs (Amendment) Ordinance.⁶⁴ In 1961, the Attorney General of California “openly cited the need for increased control of Percodan, stressing that the drug was creating a new class of addicts composed of otherwise honest, not criminally inclined persons.”⁶⁵

⁵⁷ *Id.*

⁵⁸ *Id.*

⁵⁹ *Id.*

⁶⁰ *Id.*

⁶¹ Kalso, Eija. (2005). Oxycodone. *J Pain Symptom Manage.* 29(5 Suppl):S47-56.

⁶² *The History of Opiates*, Michael’s House, <https://www.michaelshouse.com/opiate-rehab/history-of-opiates/> (last visited Sept. 21, 2018).

⁶³ *See* <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=085106>.

⁶⁴ *Oxycodone*, www.cesar.umd.edu/cesar/drugs/oxycodone.asp (date last visited Sept. 21, 2018).

⁶⁵ *Id.*

72. In 1970, Congress passed the Controlled Substances Act (CSA).⁶⁶ The Act established five schedules that classify substances according to “how dangerous they are, their potential for abuse and addiction, and whether they possess legitimate medical value.”⁶⁷ The drugs at issue in this Report are scheduled as Schedule II drugs, meaning they have a “high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous.”⁶⁸

73. Extended-release opioid products, such as controlled-release morphine sulfate products MS CONTIN and Kadian and controlled-release fentanyl products, were positioned as for use in limited circumstances. Nonetheless, reports and articles on the abuse of controlled release opioids began appearing within a few years of when these drugs began hitting the market in the late 1980s. In 1990, only three years after MS CONTIN was approved, an article was published highlighting the drug’s abuse potential.⁶⁹ The article noted that in areas such as Cincinnati, MS CONTIN had surpassed hydromorphone 4-mg tablets as the most abused prescription opioid.⁷⁰ A 1993 study on the abuse potential of opioids found that 85% of the addicts surveyed had used controlled-release morphine.⁷¹

⁶⁶ *DEA History in Depth 1970-1975*, DEA, <https://www.dea.gov/sites/default/files/2018-07/1970-1975%20p%2030-39.pdf> (date last visited Sept. 21, 2018).

⁶⁷ *Id.*

⁶⁸ *Drug Scheduling*, DEA, <https://www.dea.gov/drug-scheduling> (date last visited Sept. 21, 2018). Hydrocodone combination products, such as Vicodin, were originally scheduled as Schedule III drugs with moderate to low potential for physical and psychological dependence. As of October 6, 2014, hydrocodone combination products are now Schedule II drugs. Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II, 79 Fed. Reg. 163, 49661-49682 (Aug. 22, 2014), https://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0822.htm

⁶⁹ Crews, JC, Denson DD, Recovery of morphine from a controlled-release preparation. A source of opioid abuse. *Cancer*. 1990 Dec 15;66(12):2642-4.

⁷⁰ *Id.*

⁷¹ Brookoff D, Abuse potential of various opioid medications. *J Gen Intern Med*. 1993 Dec; 8(12):688-90.

74. The lessons learned in the early 20th Century regarding the risks of opioid abuse were pushed aside by the aggressive marketing of a new generation of opioids starting in the 1990s, and opioid manufacturers' understatement of their risks and overstatement of their benefits as set forth below.

V. PURDUE

A. Overview

75. Purdue has promoted and sold various opioid products, including MS Contin and OxyContin.⁷²

76. OxyContin is oxycodone in an extended release (ER) tablet, and oxycodone is a full opioid agonist that is relatively selective for the mu receptor.⁷³

77. Purdue received initial FDA approval to market OxyContin on December 12, 1995. A discussion of subsequent labeling changes, including approval of OxyContin reformulated, is contained in Schedule 12.

78. In reviewing OxyContin, the FDA Medical Reviewer, Dr. Curtis Wright, IV, approached the review as evaluating an existing drug with a new dosage form. Oxycodone had been on the market as a stand-alone and combination drug that was administered every four to six hours. As noted in the above historical background section, the 1980s and 1990s saw the development of extended release delivery forms for a number of drug entities, including opioids. The review of the OxyContin NDA thus focused primarily on whether the twelve-hour administration was equivalent to the shorter acting immediate-release oxycodone formulation. The longest controlled clinical studies that were submitted as part of the OxyContin NDA were

⁷² Other opioid products marketed by Purdue include Butrans, Dilaudid, Dilaudid-HP, Hysingla ER, Targiniq ER.

⁷³ PPLPC018001498098 at 3.

for fourteen days.⁷⁴ Dr. Wright concluded that OxyContin was similar in efficacy and safety to immediate release oxycodone.⁷⁵

79. Notwithstanding that FDA's review primarily focused on the safety and efficacy of this new dosage formulation, Purdue engaged in a marketing and promotional strategy "to change the way pain is treated in America."⁷⁶

80. Prior to the marketing of OxyContin, certain individual healthcare providers, such as Drs. James Campbell, June Dahl, Kathleen Foley, Michael Miller, and Russell Portenoy, advocated for improved pain assessment and treatment. However, Purdue's marketing and promotion focused on expanding the market for strong opioids.⁷⁷

81. Purdue acknowledged in 2001 that its promotional activities "contributed to a paradigm shift."⁷⁸

82. This paradigm shift expanded the use of opioids in treating pain,⁷⁹ and the concomitant increase in sales of OxyContin and opioid products in general produced *ipso facto* more opioid drugs in interstate commerce.

⁷⁴ PURCHI-000667209 at 41.

CLINICAL STUDIES					
Study Name	Indication	N	Comparison	Duration	PK/PD?
<u>Controlled Trials</u>					
OC91-0402A	CANCER	57/54	CR V. IR	5 DAY + / -	
OC91-0402B	CANCER	81/83	CR V. IR	5 DAY + / -	
OC93-0202	CANCER	50	CR V. IR	7 DAY X/O	PK/PD
OC92-1102	CA	44/44/45	10.20 CR V. PLC	14 DAY	PK/PD
OC92-1201	LOW BACK	57	CR V. IR	7 DAY X/O	PK/PD
OC88-1105	POSTOP	30/30/30	10.20.30 CR	SINGLE DOSE	none
		30/31/31	IR. PLC PCT		

⁷⁵ PURCHI-000667209 at 39, 52-53.

⁷⁶ PKY181297965 at 1.

⁷⁷ The elements of Purdue's marketing and promotion that focused on expanding the market for strong opioids were investigated and summarized by the United States General Accounting Office in 2003.

⁷⁸ PDD1503491667 at 1; *see also* PPLP003409951, PPLP003541889, PPLP004001344.

83. It is axiomatic that the more controlled substance drugs in interstate commerce, the more diversion and abuse of those drugs. Dr. Wright noted this about opioids in an article that he and other colleagues published after he left FDA and began working at Purdue.⁸⁰

84. As set forth below,⁸¹ Purdue's marketing campaign for strong opioids was extensive, misleading, and reframed the risks and benefits of not only OxyContin but opioids in general, without substantial evidence.⁸² As a result of Purdue's false and misleading promotional strategies, Purdue increased the likelihood of mis- and over-prescriptions of opioids, inadequate medical care, and the presentation of avoidable risks, such as the risk of abuse, addiction, and overdose.

⁷⁹ In Purdue meeting minutes from an April 23, 2001 meeting between Purdue and FDA, Purdue agreed that there had been a "shift in prescribing patterns" from malignant to non-malignant pain conditions, including a ten-fold increase in OxyContin prescriptions as compared to extended-release morphine:

It was noted, from 1995 to present there had been a shift in prescribing patterns out of oncology specialties into family practitioners and, when looking by indication, mentions of neoplasm were decreasing and musculoskeletal disease were increasing. Musculoskeletal disease included such terms as lumbago, myalgia and other back pain related terms. Dr. Pollock compared the number of mentions in IMS of OxyContin to MS Contin and noticed that while MS Contin prescribing had remained relatively constant, OxyContin had increased 10 fold. The Agency implied that this was a trend they were concerned with. Mr. Friedman noted that these observations were consistent with our understanding of the data we have seen.

PURCHI-000675080 at 2.

⁸⁰ Dasgupta, et al. (2006). Association between non-medical and prescriptive usage of opioids. *Drug & Alcohol Dependence* 82:135-42. Indeed, as the CDC has stated in describing the opioid epidemic, "[f]rom 1999-2017, almost 400,000 people died from an overdose involving any opioid, including prescription and illicit opioids ... The first wave began with increased prescribing of opioids in the 1990s, with overdose deaths involving prescription opioids (natural and semi-synthetic opioids and methadone) increasing since at least 1999." *See* <https://www.cdc.gov/drugoverdose/epidemic/index.html>

⁸¹ The misleading promotional materials and statements discussed below are examples and do not represent an exhaustive list of such materials and statements.

⁸² For example, in a video produced by Purdue and titled "I Got My Life Back" that was duplicated in excess of 15,000 times, the physician/narrator Dr. Spanos stated the following:

Now, in fact, the rate of addiction amongst pain patients who are treated by doctors is much less than one percent. They don't wear out, they go on working, they do not have serious medical side effects. And so, these drugs, which I repeat, are our best, strongest pain medications, should be used much more than they are for patients in pain.

P450_00000213 at 10.

B. Purdue's Marketing Strategy for OxyContin

85. As explained in an internal memo written more than five years before OxyContin was approved, a key rationale of Purdue for developing OxyContin was to replace MS Contin, a controlled-release morphine product marketed by Purdue that was facing generic competition. In this memo, dated July 16, 1990, Dr. Robert Kaiko, Purdue's then-Vice President for Clinical Research and inventor of OxyContin, wrote "MS Contin may eventually face such serious generic competition that other controlled-release opioids must be considered." Dr. Kaiko recommended developing a controlled release oxycodone product, which later became known as OxyContin, because "[w]hile we have reason to believe that other pharmaceutical firms are formulating controlled-release morphine and controlled-release hydromorphone, there is no evidence to date that this is being done with oxycodone. A controlled-release oxycodone is, thus, less likely to initially have generic competition."⁸³

86. Minutes from Purdue's OxyContin Project Team meeting on June 8, 1994 noted that "OxyContin tablets will be targeted at the cancer pain market. Since it is possible that multiple generic products may soon be in competition with MS Contin Tablets, we will target

⁸³ PKY183276631 at 1-2. Dr. Kaiko repeated this rationale for developing OxyContin in a June 24, 1992 meeting of Purdue's Analgesics Committee. PPLP004030121 at 7. Notably, in the 1990 memo, Dr. Kaiko also recognized the abuse potential of oxycodone, stating:

It is interesting to note, however, that in the State of Connecticut and perhaps other states, the substance abuse officials consider oxycodone combinations among the most abused of Schedule II narcotic analgesic drugs. Dr. William T. Beaver of Georgetown University, in reviewing the clinical pharmacology of combination analgesics, has considered oxycodone a "sleeping giant" in that among all of the opioid analgesics utilized in fixed combinations, oxycodone is the only one with an analgesic potential comparable to that of morphine.

PKY183276631.

patients who are currently receiving MS Contin as well as those patients thought to eventually use MS Contin Tablets.”⁸⁴

87. According to Purdue’s research, most doctors and nurses reserved MS Contin for use in the final step of the World Health Organization’s three step ladder for cancer pain treatment.⁸⁵



88. This analgesic ladder was created by WHO to promote the sequential use of drugs to achieve cancer pain relief, in the following order:

Step 1: Use NSAIDs to treat mild pain

Step 2: Use weaker opioids to treat mild to moderate pain, i.e., oxycodone and hydrocodone combinations.

Step 3: Use strong opioids to treat moderate to severe pain. i.e., morphine.⁸⁶

⁸⁴ PPLP004030223 at 2; *see also* PURCHI-003286781 at 11 (“MS CONTIN will face competition from AB rated generic competitors. As a result, one of the major strategies in launching OxyContin will be to replace all prescriptions for MS CONTIN.”).

⁸⁵ PURCHI-003286781 at 12.

89. With MS Contin used primarily for the Step 3 treatment of moderate to severe cancer pain, Purdue, according to its OxyContin Launch Plan, positioned OxyContin to replace MS Contin and expand into Step 2 of the WHO analgesic ladder:

Opioid choices in treating moderate to moderately severe pain in Step 2 have been limited by oxycodone, hydrocodone, and codeine combination products. Their short-acting duration of action provides peaks and valleys in pain control. The combination of the opioid with APAP or ASA limits the maximum dosage because of potential liver toxicity. The APAP or ASA component also has the potential to mask a fever in the cancer patient. **All these problems associated with the choice of opioid analgesics in Step 2 present an opportunity for the introduction of a single-entity, long-acting oxycodone product.**⁸⁷

90. According to this launch plan, “Fixed combination opioids (oxycodone, hydrocodone, and codeine combined with APAP or ASA) have been the drugs of choice for treating moderate to moderately severe pain cancer pain (WHO step 2). ... These products are considered primary competition for OxyContin.”⁸⁸

91. In addition to expanding into the Step 2 pain market for cancer pain, Purdue described in its OxyContin Launch Plan the plan to expand OxyContin into the non-malignant pain market, stating:

⁸⁶ Achieving Balance in National Opioids Control Policy, Guidelines for Assessment, World Health Organization, 2000 at 37.

The first step is a non-opioid medication (such as aspirin, paracetamol, or ibuprofen). If this does not relieve the pain, an opioid for mild to moderate pain (such as codeine) should be added. When an opioid for mild to moderate pain in combination with a non-opioid medication does not provide effective analgesia, then an opioid for moderate to severe pain (such as morphine or one in the therapeutic group of morphine) should be substituted. Adjuvant drugs should be given at any point during drug treatment to relieve adverse effects of analgesics, to enhance pain relief, and to treat concomitant psychological disturbances such as insomnia, anxiety, and depression.

Id.

⁸⁷ PURCHI-003284938 at 2 (emphasis added).

⁸⁸ *See id.* at 3.

As soon as enough appropriate clinical studies are available for promotional claims, OxyContin will be launched into the chronic non-malignant pain market. The most common diagnoses for non-malignant pain are musculoskeletal pain, injury and trauma pain. The major competitors for these diagnoses will be oxycodone and hydrocodone combination products. OxyContin will be positioned as providing the equivalent efficacy and safety of oxycodone combinations, with the benefit of a q 12h dosing schedule.⁸⁹

92. This was not Purdue's first discussion about expanding OxyContin into the non-malignant pain market. In a June 24, 1992 meeting of Purdue's Analgesics Committee, Dr. Kaiko presented options for positioning OxyContin (then referred to as Oxycodone Acrocontin) in the United States market. The first option "envisaged using Oxycodone ACROCONTIN Tablets over the entire spectrum of pain in patients whose treatment had been initiated with this product."⁹⁰

93. According to Purdue's OxyContin launch plan, expanding into the Step 2 malignant pain market and the non-malignant pain market represented a potential Class II opioid market of \$462 million and a potential Class III opioid market of \$421 million.⁹¹

94. Similarly, Purdue's then-Group Vice President of Marketing & Sales, Michael Friedman wrote a "VERY CONFIDENTIAL" memo on December 29, 1994—the day after Purdue submitted the New Drug Application for OxyContin⁹²—discussing how OxyContin could be expanded into the non-malignant pain market:

⁸⁹ See *id.* at 16; see also PPLP004030223 at 2 (identifying future non-malignant pain markets for OxyContin as including "musculoskeletal pain (back pain, osteoarthritic pain), injury trauma, and post-operative").

⁹⁰ PPLP004030121 at 7; see also PPLP004026832 at 5.

⁹¹ PURCHI-003284938 at 7-8.

⁹² PURCHI-000572404. Notably, in describing the development of OxyContin in the NDA, Purdue focused on the cancer pain market and did not address use of OxyContin for non-malignant pain:

Oxycodone hydrochloride is an opioid analgesic which has been in human use since 1915. In the United States oxycodone-containing products have been marketed for a number of years. While oxycodone/acetaminophen and oxycodone/aspirin oral dosage forms represent the bulk of

If we consider the [W.H.O.] analgesic ladder as a continuum along which we position each of the products that we propose for development, the following is how we would position our proposed development program:

1. MS Contin currently covers most of Step 3 and reaches into Step 2. Eighty percent of the use of MS Contin is in cancer, however, over one-third of the prescription are written by FPs [Family Practitioners] / GPs [General Practitioners] & IMs [Internal Medicine]. We will continue aggressive promotion of MS Contin.
2. OxyContin will cover most of Step 3, all of Step 2 and could reach down into Step 1. We expect our initial promotion of OxyContin to be directed at current prescribers of single-agent opioids and oxycodone combinations; however we will not limit our promotion of OxyContin to cancer pain. We expect that over time the FPs/GPs & IMs that prescribe the drug for cancer pain will use the drug for other types of pain. We will direct this movement through the use of clinical studies, some of which will be available shortly after launch. We hope that the use of OxyContin will expand beyond the FP/GP & IM group into the other physician groups that use oxycodone combination and Class III drugs for post-operative, musculoskeletal, injury trauma, CNS, and other pain. OxyContin will be promoted at launch with most of our sales and marketing resources.⁹³

95. Likewise, in meeting minutes from the April 4, 1995 OxyContin Launch Team Meeting, Purdue's Head of Marketing, Mike Innaurato, stated that "OxyContin's primary market positioning will be for cancer pain and the secondary market will be for non-malignant pain

oxycodone prescriptions, **oxycodone immediate-release tablets (5 mg) and oral solution (5 mg/mL and 20 mg/mL) are available and have been used in the treatment of chronic cancer pain** (Glare and Walsh, 1993). The Purdue Frederick Company has experience in marketing analgesic products (Trilisate Tablets/Liquids, DHCplusTM Capsules and MS Contin Tablets). **Experience in the chronic cancer pain market with MS Contin led to the development of a second generation Contin product for patients who could not tolerate MS Contin or who preferred to remain on oxycodone as the dose requirement increased. The result was OxyContinTM Tablets** (oxycodone hydrochloride controlled-release tablets). This product employs a modification of the MS Contin controlled-release technology called ACROCONTINTM

Id. at 246 (emphasis added).

⁹³ PPLP004030154 at 6-7.

(musculoskeletal, injury and trauma).” He further “reinforced that we do not want to niche OxyContin just for cancer pain.”⁹⁴

C. Purdue Promoted OxyContin in a Manner that Understated its Risks, Overstated its Benefits, and for Indications that Lacked Substantial Evidence to Support Safety and Efficacy.

96. According to a December 29, 1994 internal Purdue memo, moving OxyContin into the non-cancer pain market would open OxyContin up to millions of new prescribing opportunities:

It is not unreasonable to assume that the first target for OxyContin will be the 1.5 Million prescriptions currently generated for single-agent opioids, followed by the 900,000 prescriptions currently written for cancer patients using oxycodone combinations. This approach will lead to greater use by physicians for the patients receiving the other 10+ Million prescriptions for oxycodone combinations, for other indications. If price does not become a significant barrier, market expansion into chronic non-malignant pain could lead to the use of OxyContin in the 68.7 million prescription Class III market.⁹⁵

97. To do so, according this same internal Purdue memo, entailed making physicians comfortable with the use of OxyContin in place of oxycodone combinations, such as Percocet, and building credibility with two groups of doctors: (1) oncologists and (2) family practitioners, general practitioners, and internal medicine physicians:

If physicians perceive OxyContin as controlled-release Percocet it is likely that they will start to use it in place of oxycodone combinations. As physicians become more comfortable with use in the oxycodone combination market it is possible that they will also start to use OxyContin in place of Class III hydrocodone or codeine combination drugs....

The port of entry to the oncology market will be oncologists and those FPs/GPs/IMs that currently treat cancer patients. By targeting both of these groups we will establish credibility in the Oncology market. The use of

⁹⁴ PPLP004030253 at 1 (emphasis in original).

⁹⁵ PPLP004030154 at 4-5.

OxyContin in Cancer pain patients, initiated by their Oncologists and then referred back to FPs/GPs/IMs, will result in a comfort level that will enable expansion of use in chronic non-malignant pain patients also seen by the family practice specialists. As we build clinical literature and the FDA becomes more comfortable with our promotion we will be in a position to move our promotion more aggressively into the indications currently reserved for oxycodone combinations and Class III combinations, specifically post-operative pain, musculoskeletal pain, injury/trauma, and CNS pain.⁹⁶

98. A year later, after receiving initial FDA approval for OxyContin, Purdue instructed its sales representatives to aggressively promote OxyContin, noting in a December 17, 1995 OxyContin memorandum that “OxyContin will be the most promoted product in Purdue history.”⁹⁷

99. In my opinion, this aggressive promotion targeted the groups of doctors identified in Purdue’s internal memo, and as explained below, utilized promotional tactics that misbranded OxyContin as a drug that is safer and more effective than it actually is without substantial evidence.

1. Purdue’s Promotion of OxyContin and Opioids in General Minimized the Risks of Abuse, Addiction, Tolerance, and the Effects of Withdrawal.

(a) Purdue’s Marketing Misleadingly Minimized the Similarities Between OxyContin and Morphine.

100. OxyContin is and always has been pharmacologically similar to morphine, including with respect to abuse liability.

100.1. In the NDA for OxyContin, Purdue stated “Oxycodone is an opioid with pharmacologic actions similar to morphine.”

⁹⁶ *Id.*; see also PKY180544129 at 428 (Purdue’s market research anticipated that “a comfort level will be established among FPs [Family Physicians] which could expand to include OxyContin for selected non-cancer pain.”).

⁹⁷ PKY180242947 at 2.

100.2. FDA's Pharmacology Review of the OxyContin NDA concluded that OxyContin is "pharmacologically similar to morphine."⁹⁸

100.3. FDA's Medical Officer Review found that the "distribution of adverse events by body system for CR Oxycodone [OxyContin] is similar to that reported for morphine sulfate."⁹⁹

100.4. The initial OxyContin label stated "OxyContin is a mu-agonist opioid with abuse liability similar to morphine."¹⁰⁰

100.5. The current label for OxyContin contains similar language.¹⁰¹

101. Purdue's pre- and post-approval market research identified a negative "stigma" associated with morphine as to addiction.

101.1. At an OxyContin Investigator's Meeting in June 1995, results from an opioid stigma survey were reported, noting that "among health care providers there is a perception that patients feel a 'stigma' associated with opioid analgesic therapy.

Morphine and hydromorphone are most associated with this stigma. One of the patients' biggest fears appears to be the possibility of addiction..."¹⁰²

⁹⁸ PURCHI-000667209 at 140.

⁹⁹ PURCHI-000667209 at 34.

¹⁰⁰ SHC-000006346 at 6. Notably, FDA approved OxyContin for an indication similar to that of Purdue's extended-release morphine product, MS CONTIN. *See id.* at 3 ("OxyContin is intended for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days.") *compare* MS Contin Label, Jan. 28, 1994, PDD1715073161 at 1 ("[I]ndicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days."); *see also* MS Contin 1996 PDR at 2.

¹⁰¹ *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022272s040s0411bl.pdf (last visited March 15, 2019).

¹⁰² PKY181823986 at 17; PPLP004030121 at 2; PPLP004030223 at 2; PPLP004030214 at 9; SHC-000004120 at 62.

101.2. This “stigma” was confirmed in focus groups paid for by Purdue and comprised of doctors and nurses in multiple fields, which reported that “there is no question that morphine has a negative stigma with patients relative to both addiction and the terminal nature of their illness.”¹⁰³

101.3. The 1996 OxyContin Formulary Kit copyrighted by Purdue repeated this conclusion, stating “[m]isapprehension concerning the risk of addiction and poor understanding of the concepts of tolerance and physical dependence are part of the problem... Morphine bears a disproportionate share of the stigma associated with opioids, which is intensified by the drug's historic association with terminal disease and helplessness, and with the opium ‘taboo.’”¹⁰⁴

101.4. In a May 28, 1997 email from Purdue’s Michael Friedman to Dr. Richard Sackler, Friedman described the “personality” of OxyContin as being weaker than morphine:

[W]e are well aware of the view, held by many physicians, that oxycodone is weaker than morphine. We all know that this is the result of their association of oxycodone with less serious pain syndromes. This association arises from their extensive experience with and use of oxycodone combinations to treat pain arising from a diverse set of causes, some serious, but most ‘less serious.’ This ‘personality’ of oxycodone is an integral part of the ‘personality’ of OxyContin.”¹⁰⁵

102. The marketing proposals received by Purdue to develop the OxyContin brand recommended utilizing the morphine stigma to gain a competitive advantage for OxyContin.

¹⁰³ PKY181004545 at p. 23; *see also* SHC-000001965 at 2; SHC-000026456 at 46; PKY181004480 at 32; PKY181386644 at 34.

¹⁰⁴ ABT-MDL-KY-0002826 at 11.

¹⁰⁵ PPLP004030150 at 1.

102.1. One advertising agency submitted a proposed brand strategy on April 25, 1994 that highlighted the stigma attached to morphine, asking “how can we capitalize on the perception among patients and physicians that OxyContin does not carry the stigma of morphine through indirect means.” The plan emphasized that one of the “emotional advantages” of OxyContin was that there was “no morphine stigma relating to perception about addiction, tolerance, excessive power, end stage treatment.”¹⁰⁶

102.2. Other advertising agencies similarly proposed brand plans that highlighted the need to differentiate OxyContin from morphine, with one advertising agency recommending that Purdue “separate OxyContin from the ‘addiction’ stigma of morphine-containing products”¹⁰⁷ and another agency noting that the “fear of morphine addiction on the part of patients is a real barrier to treatment of pain. Because of the social issues, people would prefer to take 40 mg of oxycodone rather than 5 mg of morphine.”¹⁰⁸

102.3. In May of 1994, Purdue hired the advertising agency Lavey/Wolff Swift, Inc.,¹⁰⁹ whose proposed brand strategy highlighted that “oxycodone does not carry the stigma or many of the side effects of morphine or other third-step opioids....”¹¹⁰

103. Purdue’s marketing of OxyContin utilized the “stigma” associated with morphine to differentiate OxyContin from morphine, despite their well-known similarities.

¹⁰⁶ PKY180286806 at 11, 13, 38.

¹⁰⁷ PKY180286896 at 39-40.

¹⁰⁸ PKY180287212 at 3.

¹⁰⁹ PKY180250286 at 5.

¹¹⁰ PKY180286723 at 58.

103.1. In the same May 28, 1997 email described above, Friedman explained to Dr. Sackler how Purdue used this “personality” of OxyContin being weaker than morphine in its marketing, writing:

When we launched OxyContin, we intentionally avoided a promotional theme that would link OxyContin to cancer pain. We specifically linked OxyContin to the oxycodone combinations with our “old way, new way” campaign. We made sure that our initial detail piece provided reps with the opportunity to sell the product for a number of different pain states.¹¹¹

103.2. Friedman continued, “it would be extremely dangerous, at this stage in the life of this product, to tamper with this ‘personality,’ to make physicians think the drug is stronger or equal to morphine.”¹¹²

103.3. The following month, on June 22, 1997, Purdue’s Marketing Group Manager for OxyContin, Michael Cullen, reminded the OxyContin product team of the “perception” of OxyContin as weaker than MS Contin and stressed importance of not changing this “perception” in promotional materials:

Since oxycodone is perceived as being a “weaker” opioid than morphine, it has resulted in OxyContin being used much earlier for non-cancer pain. Physicians are positioning this product where Percocet, hydrocodone, and Tylenol with Codeine have been traditionally used.

Since the non-cancer pain market is much greater than the cancer pain market, it is important that we allow this product to be positioned where it currently is in the physician's mind. If we stress the “Power of OxyContin” versus morphine, it may help us in the smaller cancer pain market, but hurt us in the larger potential non-cancer pain market. Some physicians may start positioning this product where morphine is used, and wait until pain is severe before using it.

...

¹¹¹ PPLP004030150 at 1.

¹¹² *Id.*

It is important that we not change the position perception of physicians towards oxycodone when developing promotional pieces, symposia, review articles, etc.¹¹³

103.4. In a June 16, 1997 marketing and sales update, Michael Cullen reminded the OxyContin team that “we can show that we are as ‘effective’ as morphine, but do not want to say OxyContin is as ‘powerful’ as morphine. Words such as ‘powerful’ may make some people think the drug is dangerous and should be reserved for the more severe pain.”¹¹⁴

104. According to Purdue’s marketing team, by differentiating OxyContin from morphine, Purdue was able to expand OxyContin beyond the cancer pain market.

104.1. As noted by Michael Friedman in his email to Dr. Sackler on April 22, 1997, “despite our initial uncertainty, we have been successful beyond our expectations in the non-malignant pain market. Doctors use the drug in non-malignant pain because it is effective and the ‘personality’ of OxyContin is less threatening to them, and their patients, than that of the morphine alternatives.”¹¹⁵

104.2. In another email to Dr. Richard Sackler, Friedman explained that Purdue used this “personality” of OxyContin being weaker than morphine to differentiate OxyContin from MS CONTIN with great success:

Oxycodone has a ‘personality that is influenced by many years of oxycodone use in Percocet. We have built a large part of our platform on this personality and used it to differentiate OxyContin from MS Contin and This differentiation has lead [sic] to much non-malignant business. Marketing is not only about who you are. It is also about what

¹¹³ PPLP004032323 at 4.

¹¹⁴ PPLP004030366 at 1. To that effect, in a sales PowerPoint titled “OxyContin Competitive Market,” Purdue described morphine as “the most potent analgesic” despite OxyContin being more potent than morphine. *See* SHC-000000508 at 37

¹¹⁵ PPLP004030150 at 1.

you are not. We have a success beyond our expectations that is, in part, due to the unique personality of OxyContin.”¹¹⁶

104.3. Years later, on January 25, 2001, Friedman confirmed the success of Purdue’s strategy to distinguish OxyContin from morphine in an email to Mark Alfonso, Purdue’s Executive Director of Marketing, stating that “we were able to convince doctors to use OxyContin tablets because of its position in the doctors mind that is [sic] very different from morphine.”¹¹⁷

105. In my opinion, Purdue’s marketing minimized the similarities between OxyContin and morphine.

(b) Purdue Falsely Marketed OxyContin as Having a Lower Potential for Abuse as Compared to Other Opioid Products

106. Purdue’s early market research also identified the “**biggest negative** of the product [OxyContin] **was the abuse potential**...this was exacerbated by the fact that some felt that Q12h dosing and the lack of APAP or ASA, might make the product more susceptible to addiction.”¹¹⁸

107. To address the reluctance of physicians to prescribe OxyContin for non-cancer pain, market researchers recommended that “Purdue Frederick implement clinicals with OxyContin among non-cancer pain patients to determine if there might be any reductions in side effects that one might get when compared with the combination opioids,” noting that “[i]f the

¹¹⁶ PPLP004030162 at 1.

¹¹⁷ PPLP004030463 at 1.

¹¹⁸ PPLP004031668 at 39. In a December 3, 1996 report titled “OxyContin Research: Self-Administered Questionnaire Among Rheumatologists Prescribers and Non-Prescribers of OxyContin,” which was commissioned by Purdue, it was shown that the most frequently mentioned reason for why a physician would not prescribe OxyContin was “abuse potential (22%).” SHC -000007578 at 3.

product was proven to have a lower abuse potential than IR [immediate release] oxycodone, it would improve the likelihood of usage for non-cancer pain.”¹¹⁹

108. Purdue never conducted a clinical trial specifically evaluating, much less providing substantial evidence, that OxyContin had a lower abuse potential as compared to immediate release oxycodone or any other opioid product.¹²⁰

108.1. In 1993, Purdue conducted a “spoon and shoot” study to determine what constituents could be extracted by grinding OxyContin into a solvent traditionally used by addicts. Purdue and FDA acknowledged the ease in which Oxycodone HCL could be easily extracted in water, “a fact which abusers would most likely learn very quickly.”¹²¹

108.2. Purdue conducted a 4-year registry study, OC97-0302, that evaluated, among other things, instances of drug abuse among patients taking OxyContin.¹²² “Of the 233 subjects who enrolled in OC97-0302, 13 subjects were indicated by the investigators as having signs of ‘drug seeking behavior’ on the case report form.”¹²³ A review by the External Advisory Board (EAB) overseeing the RADARS System (Researched Abuse, Diversion, and Addiction-Related Surveillance System) reduced the number of subjects to 6.¹²⁴ Based on this reduced number, Purdue concluded that “the frequency of ‘drug seeking behavior’ cases that were considered positive or possible for drug abuse or dependence in this study” was no different than the prevalence of drug abuse in the

¹¹⁹ PPLP004031668 at 58. The recommendation by market researchers aligned with the recommendation by FDA that Purdue conduct a long-term OxyContin study of “highly selected” patients with osteoarthritis to examine, among other things, the abuse liability of OxyContin. SHC-000002018 at 1.

¹²⁰ PDD1701345999 at 1-2.

¹²¹ SHC-000007033 at 9.

¹²² See SHC-000007763 at 26

¹²³ See PDD8013445789 at 3223-3224.

¹²⁴ *Id.*

general population based on reports to the National Household Survey on Drug Abuse (NHSDA).¹²⁵

109. In addition, in 1992, 1994, and 1997, Purdue acknowledged that the question of whether OxyContin's extended release design reduced the abuse liability of the drug had not been studied.

109.1. In draft OxyContin labels from 1992 and 1994, Purdue wrote that "parenteral oxycodone has comparable abuse liability to parenteral morphine" and "whether or not the controlled-release dosage form" of OxyContin "would have the same effect is unstudied at present."¹²⁶

109.2. On February 27, 1997, after learning that Purdue was considering selling OxyContin in Germany as an uncontrolled "non-narcotic," which would eliminate the requirement to track instances of abuse, Purdue's then-Vice President of Clinical Research and the inventor of OxyContin, Dr. Robert Kaiko, responded:

b) I don't believe we have a sufficiently strong case to argue that OxyContin has minimal/or no abuse liability:

- in the U.S. oxycodone containing products were once less controlled than now; abuse resulted in greater controls;
- oxycodone containing products are still among the most abused opioids in the U.S.; this information is available to BfArM;
- the local tissue necrosis that can result from injection of OxyContin "fixed" for such abuse is not likely to be a deterrent to abuse; let us not forget that in New Zealand, MST is the most common sources of parenterally abused morphine/heroin;
- **our dossier acknowledges a small handful of patients in our research program who were suspect in terms of their drug accountability;**

¹²⁵ *Id.*

¹²⁶ PDD150109445 at 12; PDD1501101593 at 18. This language was included in the draft package insert submitted by Purdue to FDA as part of the original NDA for OxyContin. See PURCHI-000621046. For reasons unknown at the time of this report, the language appears to have been deleted by FDA during the course labeling negotiations. See PPLPC024000000134; see also PPLP004030136 ("[W]e do not have any abuse liability studies.").

- we do not have a postmarketing abuse monitoring system and data base from which we could conclude that diversion/abuse is not occurring.

c) **If Oxycontin is uncontrolled in Germany, it is highly likely that it will eventually be abused there and then controlled.** This may be more damaging to OxyContin internationally than any temporarily higher sales that would be gleaned from an uncontrolled status; let us not forget the experience with buprenorphine, which was initially uncontrolled: reports of abuse in Germany, in part, eventually led to lots of bad press and controlled status; worldwide sales suffered - even where buprenorphine had been already controlled.¹²⁷

110. Moreover, FDA specifically instructed Purdue not to make claims comparing the OxyContin to other opioid products and rejected any claim of superiority over other opioid products with respect to efficacy and safety. Specifically:

110.1. In the Integrated Summary of Safety (ISS) completed by Dr. Curtis Wright, IV on May 19, 1995 as part of the FDA Medical Officer Review, Dr. Wright stated that “[t]he best conclusion is that the efficacy of [OxyContin] is equivalent to the [immediate-release oxycodone], with an adverse event profile that is as good as the [immediate-release oxycodone]. I would not allow a ‘better’ claim;”¹²⁸

110.2. Dr. Wright also noted in the ISS that “[t]he adverse experience profile of [OxyContin] is qualitatively similar to that of the parent drug, oxycodone;”¹²⁹

110.3. In the FDA Medical Office Review’s Integrated Safety of Efficacy (ISE) completed by Dr. Wright on June 19, 1995, he stated “[t]here is some evidence, both pharmacokinetic and clinical, that reduced acute opioid adverse effects may be expected

¹²⁷ PDD1701345999 at 1-2 (emphasis added).

¹²⁸ PURCHI-000667209 at 37 (original emphasis).

¹²⁹ PURCHI-000667209 at 39.

in some patients, but there is not enough evidence to support an [adverse event] superiority claim [for OxyContin] against other marketed products;”¹³⁰ and

110.4. In the ISE, Dr. Wright also noted that “[c]are should be taken to limit competitive promotion. [OxyContin] has been shown to be as good as current therapy, but has not been shown to have a significant advantage beyond reduction in frequency of dosing.”¹³¹

111. Nonetheless, Purdue’s sales representatives were trained to make misleading statements unsupported by substantial evidence that OxyContin had lower abuse potential as compared to other opioid products, utilizing this statement that was added to the initial label approved for OxyContin: “Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.”¹³²

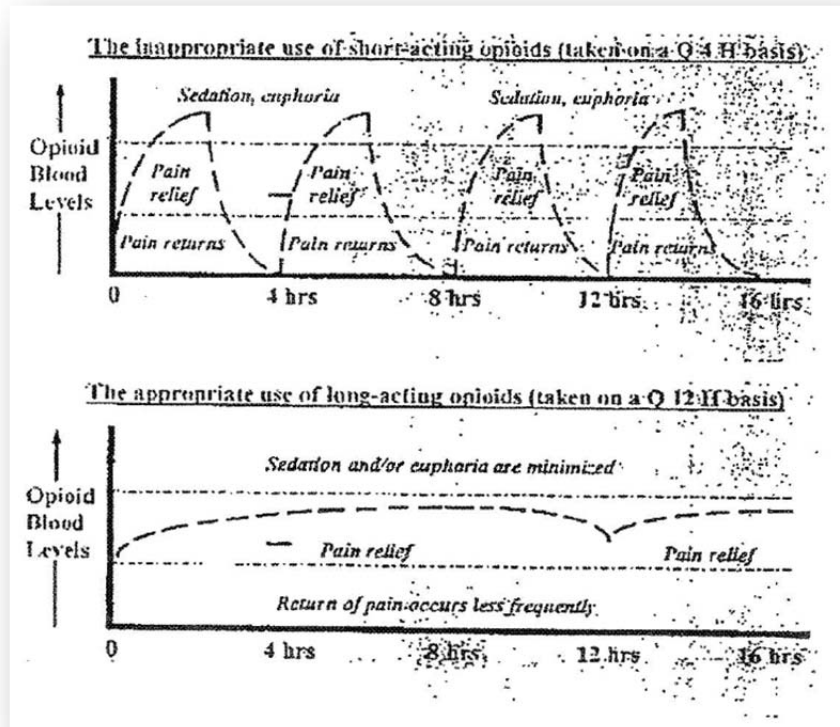
111.1. For example, Purdue held a training session in or about December 1998 for all of its district sales managers where it “falsely stated that OxyContin has significantly fewer ‘peak and trough’ blood level effects than immediate-release opioids resulting in less-euphoria and less potential for abuse than short-acting opioids” and used

¹³⁰ PURCHI-000667209 at 40.

¹³¹ PURCHI--000667209 at 53.

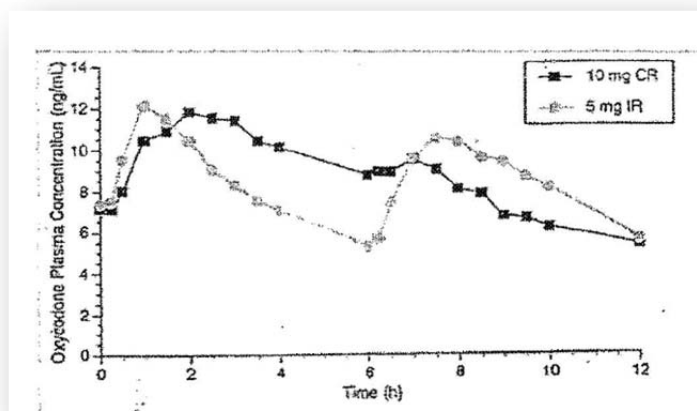
¹³² SHC-000006346 at 6. In response to media reports, Robert Reder, M.D., Purdue’s Vice President, Medical Director has stated that he believes the delayed absorption language was added by FDA. *See* Purdue Pharma Stmt on The Uncertain Hour’s OxyContin episode, December 13, 2017, *available at* <https://www.marketplace.org/2017/12/13/health-care/purdue-statement> (last visited March 15, 2019). This is contradicted by August 2, 1995 handwritten edits to the OxyContin label, which added the delayed absorption language, and were made *after* FDA reviewers submitted their labeling edits to Purdue. *See* SHC-000004520 at 19; *see also* PPLPC024000000133 (circulating FDA edits to OxyContin PI); PPLPC024000000134 (attachment to email). Further, a review of Purdue’s communications log with FDA does not reveal any contact with FDA on or near August 2, 1995 such that FDA directed Dr. Reder to add this language. *See* PPLPC001000135671. In 2001, FDA directed Purdue to remove this language from the label. *See* SHC-000008186. In the deposition of Dr. Curtis Wright, IV, he testified that “I don’t know” who proposed the language “delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.” Wright Dep. Tr. 156:16-25, 158:05-14, Dec. 19, 2018. However, Dr. Wright confirmed that the handwritten edits mentioned above were not his. *Id.* at 158:15-159:02.

the following graphical demonstration that was not based on clinical trial data and contravened a prior instruction by FDA to refer to actual data in these demonstrations:



133

¹³³ PDD1712900035 at 8-9; PURCHI-000622957 at 11-12. Below is a graph that accurately portrays the peaks and troughs by blood plasma levels for both OxyContin and immediate release oxycodone, which DDMAC instructed Purdue to use in lieu of the above promotional graphs. PDD1712900035 at 6-7.



111.2. In addition, during training at Purdue's headquarters in or around 1999, "some of PURDUE's new sales representatives were permitted ... to draw their own blood level graphs to falsely represent that OxyContin, unlike immediate-release or short-acting opioids, did not swing up and down between euphoria and pain, and resulted in less abuse potential."

111.3. In handwritten notes from a Purdue sales training that outlined responses to statements from doctors, a sales representative wrote "↑ abuse potential" in response to the statement "I prefer CIII's because I can call them in."¹³⁴

111.4. In undated sales force training materials, Purdue outlined questions to be asked of physicians misleadingly suggesting that OxyContin has low abuse potential:

9. (Using the ladder) "How would you feel about using a drug with:
a, the same indication as Vicodin and Ultram on the low end
b. with q12h dosing and **low abuse potential**
C. as your first pain medication after NSAIDs?

10. (Using the ladder): "How comfortable would you be initiating analgesic therapy after NSAIDS with a dosing regimen more mild than Tylenol #3 dosed q 4h, and **with a low abuse potential**?"

11. (Using the PDB page 24 Figure 7) "Doctor, that's excellent that you are concerned about abuse, that's exactly why the experts are using OxyContin take a look at this graph...**which drug do you think is most likely to lead to abuse potential, the one that dumps all the drug within the first hour causing this spike, or the one the enter the blood stream slowly and smoothly?**"

12. (Using the PDB page 7, last sentence in first paragraph) "Doctor, how do you feel about this statement...do your patients really set their alarm docks at midnight and 4 am? How would you feel if you could prevent this and give the patient pain prevention with **minimum abuse potential**?"

13. "Doctor, Mr. Wil Corbitt, diversion program coordinator for the DEA in the state of Florida, spoke to our group in November 1997. What do you

¹³⁴ SHC-000008102 at 2.

think he said is the biggest street abused drug in Florida? (answer: hydrocodone)...How would you feel about using a pain management tool that, according to the FDA, may have a **reduced abuse potential**?

...

15. "I am worried about my patient becoming dependent on OxyContin (or drugs like it)?" Ask the doctor, "Now do you mean dependent?" Introduce new visual aid and proper definitions Doctor, that's exactly why you should use OxyContin. Show APS page 26 ...risk of iatrogenic addiction is rare show blood levels on page 7 of PDB —Doctor, **which blood level do you think would be more likely to lead to abuse??**

...

26. If there were a pain medication that could provide 96.5% success right after NSAIDs, **with a reduced abuse liability**, how would you feel about using this product? (show package insert or product data brochure validating this success rate)

...

30. Doctor, how would you feel if one pain medication could control moderate pain right after NSAIDs as well as severe pain with a 96.5% success rate and **a reduced abuse potential**?¹³⁵

112. Aligning with the sales training provided by Purdue, Purdue's sales force falsely told health care providers in all fifty states¹³⁶ that the language in the OxyContin label regarding the possibility of reduced abuse potential "meant that OxyContin did not cause a 'buzz' or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to 'weed out' addicts and drug seekers."¹³⁷ For example, Purdue's internal call notes for OxyContin include the following misleading statements by Purdue's sales force:

112.1. May 22, 1996 (Kentucky) - "RETOLD ME THAT CLASS MADE A BIG DIFFERENCE AND **HE FELT THAT HYDORCODONE IS LESS ABUSED, AFTER HEARING THAT IT IS MUCH MORE ABUSED** AND TALKING ABOUT THE ABUSE ISSUES, HE TOLD ME THAT HE WOULD USE IT AND WOULD USE

¹³⁵ SHC-000026573 at 1-4.

¹³⁶ Shapiro Dep. Tr. 235:15-236:01, April 15, 2015, PPLP004030873.

¹³⁷ *Id.* at 210:21-211:12.

IT PREOP. I POINTED OUT THE PI, BUT HE FEELS THAT HE WOULD USE IT PREOP AS WELL AS POSTOP.”¹³⁸

112.2. November 7, 1997 (Ohio) - “ALWAYS RELUCTANT TO USE NARCS BUT TOLD IF GOING TO PUT PT ON VIC/LORT OR TYL 3, WHY NOT USE THE 12 HR DOSED, WITHOUT TYLENOL AND LESS ABUSE POTENTIAL.”¹³⁹

112.3. January 22, 1998 (Ohio) - “THOUGHT OXY WAS JUST FOR CA AND CHRONIC PAIN. TOLD LIKE Q12 HR VIC OR LORTAB/USED FOR ANY TYPE OF PAIN LASTING MORE THAN 4 DAYS.LESS ABUSE POTENTIAL”¹⁴⁰

112.4. May 21, 1998 (Ohio) - “DOES TREAT PAIN/INTERESTED IN-OXY ASKED FOR ANY PTS ON VIC/ORE THAN SEVERAL DAYS. TOLD LESS ABUSE/NO TYLENOL...”¹⁴¹

112.5. August 6, 1998 (Ohio) - “OXY FOR ALL VIC PTS/LESS ABUSE POTENTIAL AND PTS CAN SLEEP THROUGH PM.”¹⁴²

112.6. September 18, 1998 (Ohio) - DR. HAS A TON OF VICO PTS. A LOT OF LOW BACK PAIN. LEARY OF CLASS II'S. USED PI TO SELL LOW ABUSE, Q12H, AND QOFL. DR. AGREED TO USE FOR ALL OF HIS LOW BACK INSTEAD OF VICO. KEEP ON THIS GUY, THIS IS EASY MONEY.¹⁴³

¹³⁸ PPLP004032436 (emphasis added). Call notes are reproduced with minimal, if any, changes to formatting, grammar, spelling, etc., including use of all capital letters. Additional call notes can be found in Schedule 11.

¹³⁹ PKY182139780 (emphasis added).

¹⁴⁰ PKY182139597 (emphasis added).

¹⁴¹ PPLPMDL0030008507 (emphasis added).

¹⁴² PPLPMDL0030008507 (emphasis added).

¹⁴³ PPLPMDL0080000001 (emphasis added).

112.7. July 6, 1999 (Ohio) - “Hit Oxy, **does not like to prescribe narcotics because of abuse and addiction. Turned both objections into adv for Oxy.** Dr liked the fact of low abuse and drastically less tabs.”¹⁴⁴

112.8. July 15, 1999 (Ohio) - Dr. admitted that he has been seeing a ton of drug seekers lately. Has stopped giving oral opioids and will give only an injection. **Hit on low abuse and how pts. would call back screaming if they were given the Oxy in place of the Perco. Dr. agreed.**¹⁴⁵

112.9. September 20, 1999 (Ohio) - “**Dr. thinks that he is going to get busted since he is writting so much Oxy. Reminded him of less tabs and lower abuse.** Discussed using for post op pain esp those chronic painers and how to use as much Oxy to address pts. pain. Discussed tolerance.”¹⁴⁶

112.10. December 18, 2000 (Ohio) - Did get him to admit that **pts. in a LTC would be a good choice for O.C. b/c of low abuse potential** and I shared the Marcus reprint with him.¹⁴⁷

113. Purdue’s sales force likewise falsely told health care providers “that OxyContin has significantly fewer ‘peak and trough’ blood level effects than immediate-release opioids resulting in less-euphoria and less potential for abuse than short-acting opioids.”¹⁴⁸

¹⁴⁴ PPLPMDL0080000001 (emphasis added).

¹⁴⁵ PPLPMDL0080000001 (emphasis added).

¹⁴⁶ PPLPMDL0080000001 (emphasis added).

¹⁴⁷ PPLPMDL0080000001 (emphasis added).

¹⁴⁸ Attach. B to Plea Agreement of *U.S. v. The Purdue Frederick Co. Inc.*, Agreed Statement of Facts, PDD1712900035 at 6.

114. Purdue later stated that “from December 12, 1995 through June 30, 2001, Purdue marketed and promoted OxyContin as ... less subject to abuse and diversion ... than other pain medications.”¹⁴⁹

115. In my opinion, Purdue falsely marketed OxyContin as having a lower potential for abuse as compared to other opioid products.

(c) Purdue Lacked Substantial Evidence Regarding the Addictive Potential of OxyContin, Yet Misleadingly Claimed that OxyContin Was Less Addictive than Competitor Opioid Products.

116. Opioid products, including oxycodone, are addictive.

116.1. The medical literature has recognized the addictive potential of opioids.¹⁵⁰

116.2. The initial OxyContin label warned that OxyContin “may be habit forming.”¹⁵¹

116.3. Purdue acknowledged in 2001 the lack of substantial evidence regarding the rate of addiction, stating “there are no data to accurately characterize the extent of addiction” among patients taking opioids.¹⁵²

¹⁴⁹ *Id.* at 4, 5.

¹⁵⁰ *See, e.g.* Bloomquist. (1963) The Addiction Potential of Oxycodone (Percodan). Reports on Drugs. 99:2; Bouckoms et al. (1992) Chronic Nonmalignant Pain Treated with Long-Term Oral Narcotic Analgesic. Annals of Clinical Psychiatry. 4:3; Fishbain et al. (1992). Drug Abuse, Dependence, and Addiction in Chronic Pain Patients. Clinical J Pain. 8:77-85.

¹⁵¹ *See, e.g.*, SHC-000006346.

¹⁵² SHC-000020630 at 10. Notably, published historical clinical experiences with opioids indicated that iatrogenic addiction was not rare among patients using opioids for prolonged periods of time. *See* Portnow J. (1985). Medically Induced Drug Addiction. Intl J Addict 20:605-611 (“Medically induced drug addiction as a complication of medical treatment is being increasingly recognized as a widespread problem demanding new and innovative solutions.”); Musto D. (1985). Iatrogenic Addiction: the problem, its definition and history. Bull NY Acad Med 61:694-705; Walker L. (1978). Iatrogenic Addiction and Its Treatment. Intl J Addict 13:461-473.

117. From pre-approval market research conducted in 1994 and 1995, Purdue learned that “[t]he medical community is looking for a product that would be efficacious for severe pain, **particularly if it could avoid the . . . addictive potential of the opioids.**”¹⁵³

118. Despite the lack of substantial evidence regarding the addictive potential of opioids and FDA’s instruction not to make claims comparing OxyContin to other opioids,¹⁵⁴ Purdue trained its sales force to tell doctors that the addictive potential of opioids had been greatly exaggerated and that OxyContin was less addictive than competitor opioid products:

118.1. In its 1996 OxyContin launch plan, Purdue stated that “[p]hysicians, nurses and pharmacists are very often resistant to using scheduled drugs in the treatment of pain. This is due to a fear of patient drug addiction.” The plan noted that “[m]ost [physicians] are overly concerned with . . . addiction associated with opioid analgesics.”¹⁵⁵ Hence Purdue asserted in its 1996 Press Release for OxyContin that “[t]he fear of addiction is exaggerated.”¹⁵⁶

118.2. In Purdue’s 1998 marketing “War Book” for OxyContin, Purdue identified key “message points” designed to reinforce OxyContin’s advantage over competitors, one of which included OxyContin’s “low incidence of addiction or tolerance” as compared to competitors.¹⁵⁷

119. Other Purdue promotional materials downplayed the risk of addiction and were targeted at physicians.

¹⁵³ SHC-000026456 at 6 (emphasis added).

¹⁵⁴ See, e.g., PURCHI-000667209 at 36, 40, 53, 94.

¹⁵⁵ PURCHI-003284938 at 1.

¹⁵⁶ SHC-000024730 at 22.

¹⁵⁷ SHC -000004120 at 33.

119.1. On August 4, 1998, Purdue distributed to its entire sales force a sample letter to doctors on addiction. The letter downplayed the risk of addiction, stating “the risk of addiction to opioids in clinical care has been greatly exaggerated” and “[v]ery few patients taking opioids for pain fit this definition,” and instructing doctors to “look at the facts”—specifically, that:¹⁵⁸

[A] survey of more than 11,000 opioid-using patients, taken over several years, found that less than 1% (4 cases) of these patients had documented cases of addiction.

. . .

The risk of opioid abuse or addiction in patients without prior histories of abuse is extremely rare . . .

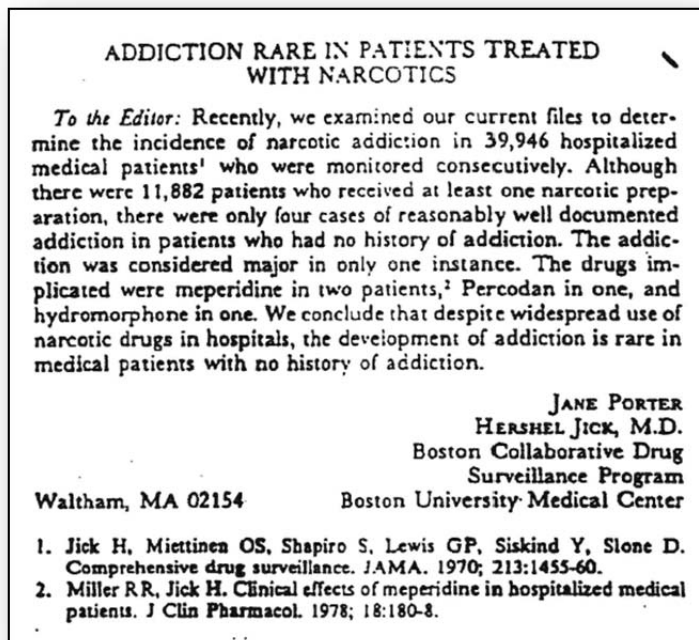
We're confident that effective pain management can be achieved in more patients if physicians like yourself look at the facts. By recognizing the fear of addiction, more and more patients can be helped with opioid therapy.¹⁵⁹

119.2. These “facts” originated from the following five sentence-long letter published by the New England Journal of Medicine in 1980 that provided no information on opioid dose, number of doses, duration of opioid treatment, extent of any long-term follow-up of patients, including whether opioid treatment was continued; or the criteria used to ascertain opioid addiction:¹⁶⁰

¹⁵⁸ PKY180117076 at 11.

¹⁵⁹ *Id.*

¹⁶⁰ Dr. Jick later admitted that he and Dr. Porter submitted the data in letter format to the New England Journal of Medicine because it was not robust enough to merit a study. *See* Barry Meir, *Pain Killer: An Empire of Deceit and the Origin of America's Opioid Epidemic* 33 (2d ed. 2018).



120. Aligning with the sales training provided by Purdue and Purdue's promotional materials, Purdue's sales force misleadingly told health care providers that opioids rarely led to addiction and that OxyContin was subject to less addiction than other opioid products, without substantial evidence:

120.1. November 19, 1997 (West Virginia) - "**CONCERNED ABOUT ADDICTION WITH OPIOIDS**. DIFFERENCE BETWEEN DEPENDENCE AND ADDICTION. **LESS THAN 1% OF PATIENTS BECOME ADDICTED**. CAN ABRUPTLY STOP LOW DOSES OF OXYCONTIN WITHOUT WITHDRAWAL SYMPTOMS"¹⁶¹

¹⁶¹ SHC-000008118 (emphasis added).

120.2. November 21, 1997 (New Jersey) - “HAS AN OPPORTUNITY TO RX PAIN MEDS IN ER AT ST FRANCIS IS CONCERNED WITH ADDICTION BUT AGREES THAT LONG ACTINGS ARE LESS LIKELY TO ADDICT”¹⁶²

120.3. April 23, 1998 (Ohio) - “RPH WAS CONCERNED WITH THE NUMBER OF PATIENTS THAT DR RICHMOND HAS PUT ON OXY, SD THEY ARE ALL PRETTY STRANGE DIS LESS ABUSE AND ADDICTION WITH OXY AND WHY MORE APPROPRIATE, DIVERSION RATE OF OXY VS OTHERS”¹⁶³

120.4. May 11, 1998 (Kentucky) - “USE OF FROM START TO WAS UNDER THE IMPRESSION THAT O WAS ONLY THERE TO REPLACE MSC. NOOOOOOO! SHOWED HIM PI INDICATION, PLUS THE NON-ADDICTIVE AND ACET PROBLEM. WHEN I LEFT HE SAID HE WAS SWITCHING THEM ALL OVER TO O FROM HYDROS WE'LL SEE.”¹⁶⁴

120.5. November 4, 1998 (Kentucky) - “BEFORE HAS A WORRY ABOUT THE DEA. TOLD HIM TO TELL THEM, IF ANYTHING EVER HAPPENED, THAT THE PURDUE REP TOLD THEM THAT IT WAS LESS ADDICTING”¹⁶⁵

120.6. March 9, 2001 (Kentucky) - “said speaker for purdue at recent FP mtg said oxy was not addicting.”¹⁶⁶

121. Purdue also created Partners Against Pain, a pain advocacy organization, to promote the claim that addiction to opioids is rare, despite lacking substantial evidence.

¹⁶² SHC-000008111 (emphasis added).

¹⁶³ PKY182142182 (emphasis added).

¹⁶⁴ PPLP004032436 at 80 (emphasis added).

¹⁶⁵ PPLP004032436 at 112 (emphasis added).

¹⁶⁶ PPLP004032436 at 401 (emphasis added).

121.1. For instance, a Partners Against Pain brochure issued in 2000 and titled “Counseling Your Patients and Their Families Regarding The Use of Opioids to Relieve Pain,” stated “a survey of more than 11,000 opioid-using patients, taken over several years, found only four cases of documented addiction” “among patients who regularly take opioids for pain, and have no history of substance abuse...which percentage represents the proportion who become addicted ... 1%.”¹⁶⁷ This brochure cited the Porter & Jick letter.

121.2. In a 2001 “Patient Bill of Rights,” Partners Against Pain stated that “[a]ddiction is very rare in patients without a history of drug/alcohol abuse when taking an opioid under a doctor’s care.”¹⁶⁸

122. Purdue also financially supported, and in some cases controlled, other pain advocacy organizations that put forth promotional materials and engaged in promotional activities that falsely claimed that the risk of opioid addiction had been exaggerated. The following is a brief summary of Purdue’s involvement in these advocacy organization and their false and misleading statements:

122.1. Purdue provided millions of dollars to pain advocacy organizations, including American Pain Foundation, Ameican Pain Society, American Academy of Pain Medicine, the Joint Commission, and the Federation of State Medical Boards.

122.2. These organizations published guidelines and other materials, provided continuing medical education, and otherwise purported to provide “education” to healthcare providers and patients regarding the safe use of opioids.

¹⁶⁷ SHC-000024493 at 11-13.

¹⁶⁸ SHC-000004944 at 5.

122.3. These promotional materials contained statements unsupported by substantial evidence and were therefore false and misleading as to the safe use of opioids, including that the rate of opioid addiction is exaggerated.¹⁶⁹

122.4. Further detail regarding Purdue's involvement in these pain advocacy organizations is provided in Section XI.¹⁷⁰

123. Likewise, Purdue acknowledged in 2007 that it "[t]old PURDUE sales representatives they could tell health care providers that OxyContin potentially creates less chance for addiction than immediate-release opioids."

124. In my opinion, Purdue's marketing misleadingly claimed without substantial evidence that OxyContin was less addictive than competitor opioid products.

(d) Purdue Misleadingly Told Health Care Providers that Patients Exhibiting Signs of Addiction Were Likely "Pseudoaddicted" and in Need of Additional Opioids to Treat Pain

125. Pseudoaddiction is a term to describe a patient who appears "looking like a drug addict" but is instead in pain and displaying symptoms of pseudoaddiction, i.e., "misinterpretation of relief-seeking behaviors as drug-seeking behaviors." It is a term that Purdue's Dr. David Haddox claimed to have coined in 1988.¹⁷¹

¹⁶⁹ See, e.g., PKY180112501 at 11. This brochure, published by Purdue's unbranded organization, Partners Against Pain, repeated Purdue's conclusion that the rate of addiction was less than 1% based on this five-sentence letter, stating "[i]n fact, a survey of more than 11,000 opioid-using patients, taken over several years, found only four cases of documented addiction. ... Many patients—and family members—will be surprised to discover that fewer than 1% of opioid-using patients become addicted!" *Id.*

¹⁷⁰ Attachment B to Plea Agreement of U.S. v. The Purdue Frederick Co. Inc., Agreed Statement of Facts, PDD1712900035 at 6.

¹⁷¹ See PPLP003877027 at 9; Weissman, D. and J. Haddox. (1989). Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 36(3): 363-66.

126. Pseudoaddiction is not supported by substantial evidence. In 2009, the American Pain Society and the American Academy of Pain Medicine, two pain advocacy organizations supported by Purdue, reviewed the claim of pseudoaddiction, finding:

We identified no systematic reviews or primary studies on accuracy of tools for differentiating drug-related behaviors due to inadequate symptom relief from true aberrant drug-related behaviors. The few studies that evaluated drug-related behaviors due to inadequate symptom relief in patients with chronic noncancer pain have not attempted to validate criteria for diagnosing this condition.¹⁷²

127. Prior to this, these and other pain advocacy organizations supported by Purdue published “educational” materials that recognized pseudoaddiction as a medical condition despite the lack of substantial evidence.¹⁷³

128. Often utilizing the materials published by these pain advocacy organizations, Purdue’s sales force promoted pseudoaddiction when physicians reported addicted patients or otherwise raised concerns about addiction to OxyContin.¹⁷⁴

128.1. April 9, 1998 (Ohio) - TALKED 3 APPROACH TO MOVING PAT OFF
OF S ACTING REM AND TOLER ACROCONT AND NO PROB WITH PH IE
ACID/ALKALINE SAME RELEASE EACH TIME. MUST TALK OXY KEYSARE
MORE PREDICTLEVELS VS ... AND REMIND HS DOSING AND PH INDEPEND
DELIV **SHOW HIM PSEUDO ADDICT AND NEED TO DOSE UP TO PAIN**
LEVEL SUGG FOR 6 PERCS LOOK AT RANGE AND INC DOSE ONE NOTCH¹⁷⁵

¹⁷² ENDO-OPIOID_MDL-01463855 at 102.

¹⁷³ See Section XI.

¹⁷⁴ A Purdue regional sales manager testified that a sales representative, when faced with a physician concerned about prescribing a higher dose of OxyContin because of addiction, should suggest the dose be adjusted upwards since the patient may be pseudoaddicted. Chris Sposato Dep. Tr. 145:5-147:19, Jan. 22, 2003, PDD9520404001.

¹⁷⁵ PPLPMDL0080000001 (emphasis added).

128.2. August 14, 1998 (Ohio) - F/U ON PHN PAT ON T3 3/DAY GO WITH 10-20 Q12H USING 10S LOOK AT HIS CONCERNS DEA/ADDICTION REVIEW PSEUDOADDICT SHOW MELNICK AND BROCHURE STRESS QOL AND PAT BENEFTITSGOOD NIGHT REST ASK FOR 1 PAT GO AFTER OSTEO NEXT¹⁷⁶

128.3. November 2, 1998 (Ohio) - CONT TO ASK FOR OXY TO BE USED FOR NEW STARTS SHOW PKGE INSERT LESS ABUSE/SHOW BLOOD LEVELS PREDICT STRESS BEST PAIN MED ON MKT MOST PREDICT ASK TO SWITCH PSEUDO ADDICTS TO OXY WANTRING EARLY REFILLS CLOSE FORE THESE PAT¹⁷⁷

128.4. June 21, 1999 (Ohio) - OXY ADDICTION VS PSEUDO, DISEASE STATE MGT AND TITRATION ISSUES COPD AND UNI VS BID THEO¹⁷⁸

128.5. February 17, 2000 (Ohio) - obj: to find out what type pain patients she is treating with oxy Action: she is treating failed back patients for the most part she actually mentioned no longer treating patients with opioid therapy because she keeps getting dinged by patients seeking we discussed pseudoaddiction vs addiction as well as the OSMA book on pain and the 5th Vital Sign I left her with an opioid documentation kit-she is not sure her mind will be changed I mentioned if she is going to choose to use an opioid, oxy is the safest one to use¹⁷⁹

128.6. November 29, 2000 (Ohio) - he is so hungry for information-went over the comfort assessment journal and empowering hispatients to take more control of their

¹⁷⁶ PPLPMDL0080000001 (emphasis added).

¹⁷⁷ PPLPMDL0080000001 (emphasis added).

¹⁷⁸ PPLPMDL0080000001 (emphasis added).

¹⁷⁹ PPLPMDL0080000001 (emphasis added).

situation-as well as how hwe is assessinf **talked pseudo addiction physocological dependence** and proper titratiom of oxycontin gave his Coles Ten tips¹⁸⁰

128.7. December 1, 2000 (Ohio) - discussed one of his patients that he dismissed from the practice because of abuse-**we discussed the source of her pain and pseudo addiction as well as psychological dependence**¹⁸¹

128.8. October 28, 2002 (Ohio) - issues here today as doing inservice are patients coming to them asking for oxycontin and **he feels they are selling it for \$80 / day** or more and just too tempting asked him what drug can he write that this can't occur **disc**... **pseudo addiction** and conntracts with patient she feels better now...¹⁸²

128.9. October 17, 2003 (Ohio) - Gave Barrett and Marsa Columbus invite. Barrett pointed out Rush story. **Reminded him that under tx can = pseudo addiction and that if not good pain doc it can and will happen**. Marsa very rushed, but says he is using as 1st choice for po long acting.....¹⁸³

129. Purdue also created the pain advocacy organization, Partners Against Pain, which promoted pseudoaddictoin, among other claims about opioids.

129.1. In 2001, Partners Against Pain provided the following definition of pseudoaddiction in a "Pain Management Kit" that was distributed to healthcare providers: "Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may 'clock watch,' and may otherwise seem inappropriately 'drug

¹⁸⁰ PPLPMDL0080000001 (emphasis added).

¹⁸¹ PPLPMDL0080000001 (emphasis added).

¹⁸² PPLPMDL0080000001 (emphasis added).

¹⁸³ PPLPMDL0080000001 (emphasis added).

seeking.’ Even such behaviors as illicit drug use and deception can occur in the patient’s efforts to obtain relief.”¹⁸⁴ Partners Against Pain repeated this definition in the 2005 and 2007 versions of its “Pain Management Kit.”¹⁸⁵

129.2. In a Partners Against Pain 2007 “Defining Key Terms in Pain Management” document, the following definition was provided for pseudoaddiction: “Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may ‘clock watch,’ and may otherwise seem inappropriately ‘drug seeking.’ Even such behaviors as illicit drug use and deception can occur in the patient’s efforts to obtain relief.”¹⁸⁶

129.3. In its 2009 Pain Management Kit, Partners Against Pain stated that the following were “behaviors [are] less suggestive of an addiction disorder,” including “aggressive complaining about the need for more drug;” “drug hoarding during periods of reduced symptoms;” “requesting specific drugs;” “opening acquiring similar drugs from other medical sources;” and “unsanctioned dose escalation...”¹⁸⁷

130. Purdue likewise supported other pain advocacy organizations to make similar misleading claims about pseudoaddiction.¹⁸⁸

¹⁸⁴ PPLP003326602 at 56.

¹⁸⁵ PPLP004114967 at 4; PPLP003341378 at 1.

¹⁸⁶ PPLP003326602 at 56.

¹⁸⁷ PKY181695113 at 53.

¹⁸⁸ See Section XI.

131. In addition, Purdue's key opinion leaders were instructed on pseudoaddiction,¹⁸⁹ and gave presentations and otherwise conveyed the concept of pseudoaddiction to healthcare providers despite lacking substantial evidence to support the claim.¹⁹⁰

132. In my opinion, Purdue misleadingly told health care providers that patients exhibiting signs of addiction were likely "psuedoaddicted" and in need of additional opioids to treat pain.

(e) Purdue Minimized the Risks of Tolerance and Physical Dependence that Patients Could Experience with OxyContin

133. Known side effects of OxyContin include "tolerance" and "physical dependence."¹⁹¹

134. "Tolerance" is "the need for increasing doses of opioids to maintain a defined effect such as analgesia," and "physical dependence" is "the occurrence of withdrawal symptoms after abrupt discontinuation of a drug."¹⁹²

135. Both conditions "are not unusual during chronic opioid therapy."¹⁹³

136. Despite this, Purdue downplayed their risks in OxyContin promotional materials provided to health care providers. For instance, Purdue's sales representatives distributed reprints of a December 1998 article published by Robert Reder, MD, Purdue Vice President and Medical Director, and Sanford Roth, MD, a rheumatologist and speaker¹⁹⁴ for Purdue, which discussed the

¹⁸⁹ PDD1503981005 at 75.

¹⁹⁰ PDD1502210202 at 827 (identifying the speaker training presentation as "accredited continuing education").

¹⁹¹ SHC-000006346 at 4.

¹⁹² *Id. see also* Phillips JK, Ford MA, Bonnie RJ. (2017). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. National Academies Press, *available at*: <https://www.ncbi.nlm.nih.gov/books/NBK458661/Phillips>.

¹⁹³ SHC-000006346 at 4 (emphasis added).

¹⁹⁴ *See* E513_00004803 at 9 (identifying Dr. Sanford as a speaker for a Purdue sponsored event); SHC-000024908 at 19 (identifying Dr. Sanford as a speaker at a Purdue symposium/luncheon).

“misconceptions” of opioids, including that “tolerance is rarely a practical problem in opioid therapy.”¹⁹⁵

137. Likewise, in promotional materials from 1996 through at least 2008, Purdue did not prominently disclose the possibility of tolerance or physical dependence to OxyContin.¹⁹⁶ Instead, Purdue focused primarily on the benefits of OxyContin.

137.1. For example, in or around December of 1996, Purdue sent to healthcare providers the following letter failed to present a fair and balanced evaluation of the risks and benefits of OxyContin by failing to disclose the possibility of tolerance or physical dependence to OxyContin:

On your formulary, q12h OxyContin can enhance pain control, because it provides:

- The analgesic efficacy of oxycodone* with the ease of q12h dosing
- Twelve hours of smooth and reliable pain control—less frequent dosing than with Percocet, Vicodin, or Tylenol with Codeine
- Analgesic onset within 1 hour in most patients
- Single-entity therapy—no aspirin or acetaminophen which may be potentially toxic in maximal daily doses
- No “ceiling” to analgesic efficacy—may be titrated upward when clinically necessary
- Diminishing side effects (except constipation) over time for many patients


OxyContin is a logical “next step” when around-the-clock (A-T-C) opioid therapy is needed. We are confident it is a logical “next choice” for your formulary.¹⁹⁷

¹⁹⁵ Sanford R. (1998). The Role of Opioids in the Treatment of Osteoarthritis. Resident & Staff Physician. 44(12):21-36, PDD1701869808.

¹⁹⁶ See, e.g., PURCHI-000550536; PURCHI-000723096; PURCHI-000723253; PURCHI-000723352; PURCHI-000723681; PURCHI-000723829; PURCHI-000723966; PURCHI-000724367; PURCHI-000763440; PURCHI-000813598; PURCHI-000830011

¹⁹⁷ PURCHI-000723253 at 70.

137.2. Similarly, the following September 18, 2003 promotional material used by Purdue as a display at a healthcare convention failed to present a fair balance of information relating to risks and benefits in that it did not prominently disclose the risks of tolerance and physical dependence to OxyContin:¹⁹⁸



For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

THERE CAN BE LIFE WITH RELIEF

- **Q12h dosing convenience**
- **Onset of analgesia within 1 hour in most patients***
- **Convenient conversion and titration**
- **OxyContin® is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. Consider this when an increased risk of misuse, abuse, or diversion is a concern**
- **OxyContin® Tablets are NOT intended for use as a prn analgesic**
- **OxyContin® TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE**
- **OxyContin® 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY.** These tablets may cause fatal respiratory depression when administered to opioid-naïve patients
- **The most serious risk with OxyContin® is respiratory depression, which can be fatal**
- **OxyContin® is not indicated for pre-emptive analgesia, pain in the immediate postoperative period (the first 12 to 24 hours following surgery) in patients not previously taking OxyContin® (because its safety in this setting has not been established), or pain that is mild or not expected to persist for an extended period of time**
- **As used here, "moderate" and "moderate to severe" pain do not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort**

* From a single-dose study.
Reference: 1. Sunshine A, Olson NZ, Colon A, et al. Analgesic efficacy of controlled-release oxycodone in postoperative pain. J Clin Pharmacol. 1996;36:595-603.

Q12h
OXYCONTIN®
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
IT WORKS

Please read professional prescribing information, including boxed warning, available at this exhibit.

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138. Purdue's pain advocacy organization, Partners Against Pain, also made statements that discussed the ability to increase the dose of opioids without adequately addressing the significant risk of doing so.¹⁹⁹

¹⁹⁸ PURCHI-000723966 at 19.

¹⁹⁹ Purdue also supported pain advocacy organizations that downplayed these risks. See Section XI.

138.1. A 2005 brochure titled “Clinical Issues in Opioid Prescribing” stated “[i]f opioid doses are gradually increased, high dosages are generally well tolerated and not associated with respiratory depression” without discussion of physical tolerance or dependence.²⁰⁰

138.2. Similarly, in the 2000 brochure titled “Counseling Your Patients and Their Families Regarding The Use of Opioids to Relieve Pain,” Partners Against Pain stated the following without discussing the associated risks with opioids “[u]nlike nonopioid pain relievers, an opioid has no “maximum” daily dose-which allows us to adjust the dose to an effective level, no matter how severe your pain” and “[r]emember, opioids are not limited to a ‘maximum’ dose as nonopioids are-an effective dose can be found for virtually any type or severity of pain.”²⁰¹

139. Even when Purdue acknowledged the risks of physical dependence in marketing OxyContin, Purdue downplayed their clinical significance. Specifically, Purdue minimized the severity of withdrawals symptoms resulting from physical dependence,²⁰² which per the OxyContin label, included restlessness, lachrymation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis, among others.

139.1. In Purdue’s 1996 sales training, Purdue stated that tolerance and physical dependence do not pose a major clinical problems and that “it is usually not difficult to withdraw an opioid when it is no longer required,”²⁰³ which Purdue’s sales force conveyed to healthcare providers.

²⁰⁰ PPLP004114967 at 6.

²⁰¹ SHC-000024493 at 7, 9

²⁰² Purdue also supported pain advocacy organizations that downplayed these risks. See Section XI.

²⁰³ ABT-MDL-KY-0008846 at 63-64.

139.2. Purdue downplayed physical dependence and its associated withdrawal symptoms at a Purdue dinner symposium at the May 1997 convention of the National Association of Orthopedic Nurses. There, according to a summary provided by a Purdue sales representative, Elizabeth Narcessian, MD, “an active member of Purdue’s Speaker’s Bureau” who helped train other speakers as well as Purdue sales representatives,²⁰⁴ provided the following information to the 510 nurses in attendance about withdrawing from OxyContin:

Dr. Narcessian used an analogy that seemed to get across the addiction vs physical dependence issue. She said that if you drink coffee regularly and stop drinking it one morning, you will most likely get a headache (a withdrawal symptom). That is physical dependence, similar to the withdrawal effect experienced when an opioid is stopped.²⁰⁵

140. Purdue also misleadingly told healthcare providers without substantial evidence that “withdrawal symptoms” from physical dependence would not occur at lower doses but “when high dose opioid therapy is suddenly stopped,”²⁰⁶ such as at doses of 60 mg/day or higher.²⁰⁷

141. Since 1999, and possibly earlier, Purdue was aware reports of withdrawal symptoms in patients stopping OxyContin at doses less than 60 mg per day, and in as early as March 28, 2001, Purdue was aware of concerns regarding the accuracy of the withdrawal data in its published osteoarthritic study.

²⁰⁴ SHC-000024908 at 12.

²⁰⁵ PKY180254414 at 3.

²⁰⁶ Sanford R. (1998). The Role of Opioids in the Treatment of Osteoarthritis. Resident & Staff Physician. 44(12):21-36, PURCH-000816988 at 21; *see also* Exhibit B to Plea Agreement of *U.S. v. The Purdue Frederick Co. Inc.*, Agreed Statement of Facts, at 9-13.

²⁰⁷ *Id.*; *see also* Sanford R. et al. (2000). Around-the-Clock, Controlled-Release Oxycodone Therapy for Osteoarthritis-Related Pain. Arch Intern Med. 160:853-860, PPLP003983624 at 7; *see also* Gasdia Dep. Tr. 248:16-22, June 27, 2008.

141.1. Purdue learned through a long-term clinical study evaluating OxyContin in osteoarthritis patients (Clinical Study OC92-1103) that physical dependence (and associated withdrawal symptoms) occur even at low doses. In this study, case report forms documented that 13 patients experienced symptoms of withdrawal during periods in which patients were instructed not to take OxyContin. Of the 13 patients, 3 withdrew during the respite period and were taking OxyContin doses less than 60 mg per day. Of the remaining 10 patients, all but two were taking doses lower than 60 mg per day.²⁰⁸ Purdue did not include these as instances of withdrawal in its final study report for OC92-1103, which it submitted to FDA on January 16, 1997.²⁰⁹

141.2. Approximately two years later, on February 12, 1999, an affiliate of Purdue²¹⁰ conducted a meta-analysis of the long-term clinical studies available for OxyContin, which included OC92-1103 and another Purdue clinical study, OC92-1101. This meta-analysis likewise identified instances of withdrawal in patients taking less than OxyContin 60 mg per day.²¹¹

141.3. After the issuance of this meta-analysis by a Purdue affiliate, Purdue—along with Dr. Sanford Roth and other clinical investigators—published the study results of OC92-1103 in a medical journal. In this published study, Purdue reported only two instances of withdrawal following abrupt cessation of doses of 60 mg/day or higher,

²⁰⁸ PPLPC024000037828 at 1-2 (identifying 3 subject who discontinued during respite because of adverse experiences due to possible withdrawal symptoms and additional 10 unique subjects who experienced adverse experiences due to possible withdrawal symptoms).

²⁰⁹ PURCHI-000566584.

²¹⁰ PKY180803001 at 8 (“Purdue Pharma LP, the US associate of Napp Pharmaceuticals Ltd.”).

²¹¹ *Id.* at 35-39.

which according to Purdue, “indicat[ed] that CR oxycodone at doses below 60 mg/d can be discontinued without tapering the dose if the patient's condition so warrants.”²¹²

141.4. Purdue utilized this published study to understate the risk of physical dependency and withdrawal; specifically:

On or about June 26, 2000, certain PURDUE supervisors and employees sent the full text of the osteoarthritis study article together with a “marketing tip” to PURDUE’s entire sales force. The marketing tip stated that a reprint of the osteoarthritis study article was available for use in achieving sales success. The marketing tip also included as one of the article's twelve key points: “There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites indicating that CR oxycodone at doses below 60 mg/d can be discontinued without tapering the dose if the patient condition so warrants.”²¹³

141.5. Purdue did not take affirmative action to correct this inaccurate information and continued to distribute reprints of the article to sales representatives, who in turn, distributed the false and misleading information to healthcare providers.²¹⁴

142. In my opinion, Purdue minimized the risks of tolerance and physical dependence that patients could experience with OxyContin.

(f) Purdue’s Marketing Minimized the Risks of Respiratory Depression, Addiction, and Abuse Associated with Higher Doses of OxyContin

143. From early market research, Purdue learned that physicians were concerned with prescribing opioid combination products, i.e., opioids combined with aspirin or acetaminophen

²¹² Roth S. et al. (2000). Around-the-Clock, Controlled-Release Oxycodone Therapy for Osteoarthritis-Related Pain. *Arch Intern Med.* 160:853-860, PPLP003983624 at 7.

²¹³ Attach. B to Plea Agreement of *U.S. v. The Purdue Frederick Co. Inc.*, Agreed Statement of Facts, PDD1712900035 at 12.

²¹⁴ *Id.* at 12-13.

such as Vicodin or Percocet, because “the toxicity limitation of the combination drugs ... precluded their use for the most severe pain, since it was not possible to give enough medicine to control the pain without putting the patient in danger.”²¹⁵ This “danger” was the concern of renal or hepatic toxicity from excess doses of aspirin or acetaminophen.

144. Purdue recognized that OxyContin, as a single-opioid agent, would not have this dose-limiting property, and in Purdue’s early market research, physicians identified “the absence of toxicity concerns as currently exist with the combination products” as an “important strength” of OxyContin and found “no dose ceiling” to be a “strong copy point” in which to market OxyContin.²¹⁶

145. Purdue highlighted this point in its promotion of OxyContin, telling physicians, for example, that “[a]s a single-entity opioid with no ceiling to analgesic efficacy, OXYCONTIN Tablets may be used at doses not limited by maximum permitted doses of NSAIDs or acetaminophen in fixed-combination products.”²¹⁷

²¹⁵ PKY181386644 at 27.

²¹⁶ *Id.* at 31, 34.

²¹⁷ PURCHI-00072320 at 24; *see also* PURCHI-00072310 at 13 (“Doses of opioid agonists such as oxycodone have no ceiling effect for analgesic activity, as evident in the wide dosage range of OXYCONTIN Tablets used in long-term clinical trials.”); *Id.* at 24 (“As a single-entity opioid with no ceiling to analgesic efficacy, OXYCONTIN Tablets may be used at doses not limited by maximum permitted doses of NSAIDs or acetaminophen in fixed-combination products.”); PURCHI-00072310 at 48 (“No ceiling to analgesic efficacy. With full agonists, such as oxycodone ‘effectiveness with increasing doses is not limited by a ‘ceiling.’ OxyContin may be dosed upward as clinically necessary.”); PURCHI-00072310 at 58 (“OxyContin has no ‘ceiling’ to its analgesic efficacy and may be titrated upward, when clinically necessary, with confidence.” (emphasis added)); PURCHI-000550536 at 38 (“Not limited by analgesic ‘ceiling’ or maximum daily dose. OxyContin may be dosed as high as clinically necessary.”); PURCHI-000672849 at 20 (“OxyContin may be titrated as high as clinically necessary, unlike analgesic products such as Percocet, Vicodin, Lorcet, Darvocet-N, and Tylenol with Codeine, or their generic equivalents. OxyContin can be titrated upwards every 24-48 hours, when clinically necessary, until an effective dose is reached, with acceptable side effects.”); PDD9316729260 at 67 (“There is added dosing flexibility with a single agent, since a variety of co-analgesics and adjuvant medications can be used to enhance the individual patient’s pain relief, while having the freedom to dose OxyContin Tablets as high as is clinically necessary.”); PURCHI-000701440 at 9 (“Consider the daily limitations. Many short-acting opioids contain a nonopioid analgesic that limits the maximum daily dose. OxyContin is a single-entity agent that does not contain acetaminophen, aspirin or ibuprofen. Ceiling to analgesic effectiveness is limited only by side effects.”).

146. In doing so, however, Purdue did not balance the significant risks associated with taking larger doses of OxyContin—namely, the potentially fatal risk of respiratory depression²¹⁸ and the increased risk of abuse.²¹⁹

147. Specifically, in marketing OxyContin, Purdue’s sales representatives emphasized that OxyContin has no dose ceiling, encouraging healthcare providers to increase the dose of OxyContin without discussing the risks associated with dose increases.

147.1. February 2, 1996 (Ohio) - BRIEFLY DISCUSSED OXY AND UNIMENTION. DISCUSSED WHO STEP APPROACH AND USE IN STEP 2 WITH OXYCODONE. AND ALSO USE IN NON MALIGNANT PAIN WITH LOWER ABUSE POTENTIAL. **STRESSED Q12H DOSING WITH OXY AND NO DOSE CEILING.** FOLLOW ON 2/12 WITH MORE DETAIL FROM PI ON OXY. FIND OUT WHERE HE SEES IT FITTING IN.²²⁰

²¹⁸ SHC-000006346 at 3; *see also* Phillips JK, Ford MA, Bonnie RJ. (2017). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. National Academies Press, *available at*: <https://www.ncbi.nlm.nih.gov/books/NBK458661/Phillips>.

²¹⁹ *See* Dunn, K.M., et al., Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*, 2010. 152(2): p. 85-92; Gomes, T., et al., Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*, 2011. 171(7): p. 686-91; Bohnert, A.S., et al., Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*, 2011. 305(13): p. 1315-21; Paulozzi, L.J., et al., A History of Being Prescribed Controlled Substances and Risk of Drug Overdose Death. *Pain Med*, 2012. 13(1): p. 87-95; Zedler, B., et al., Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients. *Pain Med*, 2014; Bohnert, A.S., et al., A Detailed Exploration Into the Association of Prescribed Opioid Dosage and Overdose Deaths Among Patients With Chronic Pain. *Med Care*, 2016. 54(5): p. 435-41; Dasgupta, N., et al., Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. *Pain Med*, 2016. 17(1): p. 85-98; Bohnert, A., et al., Understanding Links among Opioid Use, Overdose, and Suicide. *N. Engl. J. Med* 2019; 380:71-9. In addition, Purdue acknowledged in 2001 that “[t]olerance to opioids which results in a dosage increase” was a “side effect” contributing to the abuse of OxyContin and that “[p]atients would therefore benefit from the reduction of the development of tolerance ...” (emphasis added).

²²⁰ PPLPMDL0080000001 (emphasis added).

147.2. March 6, 1997 (Ohio) - LIKES OXY BECAUSE OF FEWER SIDE EFFECTS. **STRESSED NO CEILING AND 80MG.** WILL SEND LIVE W/L²²¹

147.3. January 8, 1998 (Ohio) - USING OXY FOR OSTEO AL;SO STATING WITH PHN/DN **KEEP REM TO INC DOSE NO CEILING** REMIND QOL ADV AFTER NSAID UNIPH SHOW MARTIN TELL HIM CONVERS IS RIGHT TO DOSHOW QD BETTER THAN BIDID.²²²

147.4. January 20, 1999 (Ohio) - **MUST CONT TO STRESS ADV AND ABIL TO INC DOSE NO CEILING** WANTS A 60 MG DOSE SAID HAS MANY ON 20S/40S SUGG EITHER INTERVAL DOSING WITH 40S OR SWITCH TO 80MG Q12H²²³

147.5. February 9, 1999 (Ohio) - HE IS GOOD ON DOSING **HAS NOT EXCEEDED 80 Q12H YET CONTIN TO STRESS NO CEILING BUT SEEMS TO BE COMING AROUND ON THIS ISSUE** STILL FEELS TOLER IS SEEN BETWEEN 40-80 MG MUST....²²⁴

147.6. January 28, 2000 (Ohio) - MD ALWAYS SEES ME CARRYING IN SAMPLES OF SENOKOT WHICH STARTS CONVERSATION; MD SEEMS TO BE TRULEY THANKFUL FOR THE SAMPLES THAT HE RECEIVES; **OXY DISCUSSED RE: NO CEILING DOSE AND EASE OF TITRATION;** OXY

²²¹ PPLPMDL0080000001 (emphasis added).

²²² PPLPMDL0080000001 (emphasis added).

²²³ PPLPMDL0080000001 (emphasis added).

²²⁴ PPLPMDL0080000001 (emphasis added).

IR/FAST FOR BREAKTHROUGH PAIN; CONVERSION CHARTS LEFT WITH MD FOR HIS REVIEW.²²⁵

147.7. February 23, 2000 (Ohio) - Titration call again, went over no ceiling and that 80mg is far from too much. Dr said he gets the message and said he has used the 80mg.²²⁶

147.8. July 6, 2000 (Ohio) - SPOKE WITH MD WHO EXPRESSED CONCERN RE: ONE PT RECEIVING 120 MG Q 12 FOR BACK PAIN- DISCUSSED THE PFACT THAT THERE IS NO CEILING DOSE WITH OXY LIKE SHORT ACTING; HE SEEMED TO THINK THAT THIS PT WAS ABUSING THE PRODUCT; HE NEEDS REAFFIRMATION RE: THE DECREASED ABILITY OF OXY TO BE ABUSED AND DECREASING NUMBER OF TABS....²²⁷

147.9. August 11, 2000 (Ohio) - asked r to to upgrae to the 80 mg q 12 h for difficult pat - dr. agrees - positioned oxy ir for breakthrough reminder detail to dr. on oxy - stay w message - push the high dose - sampled uni and senokot reminded dr that 160 mg tab is coming out - he asked abt oxy fast for break - does not have in southside - y-town - disc high dose pat - 40 mg q 12 h asked if he would write oxy ins of ... for diff pat - disc the inconsist of pain control w ... - asked if he would write 80mg oxy instead of ... - said he will write more oxy f reminded dr that oxy has no ceiling - that he can go above 80 mg - also the potency of oxy vs vic is =n asked dr what he does after 40 mg q 12 - he adds ... - explained the no ceiling of oxy - told him 60 -80mg q 12 is a low dose

²²⁵ PPLPMDL0080000001 (emphasis added).

²²⁶ PPLPMDL0080000001 (emphasis added).

²²⁷ PPLPMDL0080000001 (emphasis added).

of a med that has no limits - says he will go up in dose before switching - was surprised to learn that oxy is no ceiling compared to combos - asked many q about hospice pat and nurses - wanted to know what chevlen does - lots of oxy - 1--1.5 ratio less hal and naus - fu on dosing up and acute vs vic.²²⁸

147.10. January 19, 2001 (Ohio) - doc said he has been using oxy for awhile and that he uses high doses, **i reminded doc there is no ceiling and that he should not worry about how high he needs to go.**²²⁹

147.11. April 6, 2001 (Ohio) - OK w Oxy has (post op back) pt on 80mgs q 12h with Oxy IR q4 in between, talked about titrating up to 100mgs q12 h, at first said he was going to refer to Dr Chevlen, **thinks something else may be going on afraid of higher doses- told of no ceiling,** pt is coming in next week, hopefully he will give this a try before referral. Invited to Dr G's RT but staff doubtful if he will attend because he frequently works until 7:00pm.²³⁰

147.12. March 20, 2003 (Ohio) - Spoke with Dr in clinic, **Dr asked me about a max dose with OxyContin. I went over the idea of no ceiling with any single entity drug and that what actually limits combos is acet and apap.** I explained the advantage of being able to titrate to effect with out worry of acet or apap toxicity.²³¹

148. According to depositions of Purdue employees, Purdue generated greater revenue off the higher doses of OxyContin,²³² and Purdue encouraged its sales force to promote higher

²²⁸ PPLPMDL0080000001 (emphasis added).

²²⁹ PPLPMDL0080000001 (emphasis added).

²³⁰ PPLPMDL0080000001 (emphasis added).

²³¹ PPLPMDL0080000001 (emphasis added).

²³² Sposato Dep. 18:21-24, PDD9520404001.

doses of OxyContin by utilizing a unique incentive system that bonused sales representatives based on increasing dollar volume of sales and not on the number of prescriptions written as is the usual practice.

148.1. As explained by Karen White, a sales representative for Purdue from 1998 to 2002, bonusing on the increase in dollar sales meant “[i]t would exponentially affect our bonuses. I mean if we got the doctor, as I mentioned earlier, to write an 80 milligram instead of a 10 milligram, we would make seven and a half times more money based on what percentage of our sales that we increased over our quota.”²³³

148.2. As a result of this incentive structure, according to Ms. White deposition testimony, sales representatives were encouraged to call on pill mills:

[T]he other reason that I have a problem with [the incentive structure] it is that it behooved us to call on what I refer to as pill mill doctor, doctors who are inappropriately prescribing narcotics. If a Purdue representative knew from one source or another that a doctor was inappropriately prescribing and was a pill mill, a lot of times they didn't turn them in to Purdue because they were making tons of money off of these doctors prescribing OxyContin in the place of other medications. And they were typically prescribing high doses of OxyContin in a lot of cases.²³⁴

148.3. Ms. White's testimony is further supported by a 2001 internal sales memo in which Purdue highlighted to sales representatives that they should “[f]ocus on high prescribers ~ 2-4 calls per month.”²³⁵

149. In my opinion, Purdue's marketing minimized the risks of respiratory depression, addiction, and abuse associated with higher doses of OxyContin.

²³³ White Dep. 98:23-99:14, Dec. 17, 2003, PKY182895039; *see also* Sposato Dep. 18:21-19:2, PDD9520404001. (“Q. My question is: Same amount of pills, higher dosage, Purdue makes more money for the higher dosage, correct? A. That's correct. Q. And that factors into someone's bonus, correct? A. Possibly.”).

²³⁴ White Dep. 99:15-25, PKY182895039.

²³⁵ ABT-MDL-KY-0050021 at 5.

2. In Response to OxyContin Not Being Effective for 12 Hours, Purdue Developed a Strategy to Increase the Total Daily OxyContin Dose but Failed to Inform the Public, Putting Patients at Risk.

150. Based on its pre-market research, Purdue's Marketing Department reported that OxyContin would be positioned as "the only opioid combining the efficacy and safety of oxycodone with the convenience of 12-hour dosing schedule."²³⁶

151. In Purdue's clinical trial program, OxyContin did not provide 12 hours of pain relief for most patients. Specifically, in the majority clinical trials in which rescue dosing was permitted, more than half of the subjects required daily rescue dosing for the majority of treatment time.

151.1. For example, in OC92-1001, which was a double-blind, randomized, q12hr multiple-dose, parallel-group comparison of the pharmacokinetic and pharmacodynamic profiles of controlled-release oxycodone (OxyContin) and MS Contin tablets in patients with chronic cancer-related pain, "rescue use was quite infrequent (an average of one dose per day)."²³⁷ It is important to note that MS Contin was considered a Q8-Q12 hr drug. In other words, on average, 50% of the doses in both arms of this study failed.

151.2. Similarly, in OC92-1201, titled A Double Blind, Randomized, Two-Period Crossover Comparison of the Pharmacokinetic and Pharmacodynamic Profiles of Immediate-Release and Controlled Release Oxycodone in Patients with Chronic Low

²³⁶ PPLP004030214 at 1, 9.

²³⁷ PURCHI-000543673 at 28.

Back Pain, “patients required, on average, approximately 0.6 doses per day” of rescue medication.²³⁸

151.3. Similarly, in OC93-0303, titled Double-Bind, Randomized, Repeated Dose, Crossover Comparison of The Pharmacokinetic and Pharmacodynamic Profiles of Controlled-Release Oxycodone and Controlled-Release Morphine in Cancer Patients with Pain, which compared OxyContin to MS Contin in cancer patients, “the mean number of rescue doses taken by patients ... was significantly higher with CR oxycodone compared with CR morphine for the 3-day average.”²³⁹ Specifically, in this study, the OxyContin patients reported using an average of 1.43 rescue doses during the last three days of the double-blind period of the study.²⁴⁰

151.4. In OC96-0204, titled “An Open-Label Multi-Center Study to Confirm the Guidelines for the Conversion of OxyContin Tablets when Utilized for the Conversion of Post-Surgical Subjects from Intravenous Continuous Opioid Infusion (CI) and/or Patient Controlled Opioid Analgesia (PCA) to an Oral Controlled Release Oxycodone Regimen” “patients used an average of 1 dose of supplemental analgesic daily” following implementation of the OxyContin.²⁴¹

151.5. In another clinical trial, OC91-0402A, which compared OxyContin to immediate release oxycodone in patients previously stabilized on strong opioid analgesics for chronic cancer-related pain, the protocol did not permit the use of rescue dosing among patients, leading to a discontinuation of 9 of 42 (21%) OxyContin patients.

²³⁸ PURCHI-000599520 at 64.

²³⁹ PURCHI-000564151 at 68.

²⁴⁰ *Id.*

²⁴¹ PURCHI-000627156 at 5.

Among patients on the comparator arm, 4 of 36 (11%) patients were discontinued for rescue dose.²⁴²

151.6. In a similar study, OC91-0402B, rescue dosing due to ineffective treatment was not initially permitted and any patient requiring rescue medication would be discontinued from the study. “A total of 36 out of 81 (44.4%) randomized CR patients discontinued from the study: 18 (22.2%) for ineffective treatment.”²⁴³ The clinical trial protocol was then amended, and “[p]atients enrolled after Amendment II were allowed titration prior to entry into double-blind and rescue medication. With this availability the discontinuation rate due to ineffective therapy for patients receiving CR Oxycodone dropped to 3.5%.”²⁴⁴ “The overall number of rescues doses per day was 0.6 for the CR Oxycodone group...”²⁴⁵ In other words, on average, more than half of the OxyContin doses failed.

151.7. In reviewing these clinical trials, the FDA Medical Officer Review noted that “[i]mmmediate release oxycodone was used as the rescue analgesic [sic] in these studies . . . Patients used about 1-2 doses of rescue a day and found it an important part of therapy.”²⁴⁶

152. Even though Purdue’s clinical trial program demonstrated that OxyContin, absent rescue dosing, could not provide continual analgesic relief on a Q12h basis in most patients, Purdue acknowledged that prescribing OxyContin on a dosing regimen less than Q12h could

²⁴² PURCHI-000587719 at 209.

²⁴³ PURCHI-000591935 at 36.

²⁴⁴ *Id.*

²⁴⁵ *Id.* at 98.

²⁴⁶ PURCHI-000667209 at 53.

jeopardize OxyContin's position with insurance formularies who would give preference to generic opioid products at those dosing frequencies.

152.1. In a June 6, 2000 email, Purdue's Robert Vik wrote that he was "informed that a growing number of patients are being prescribed OxyContin on a Q4h – Q8h frequency. This has precipitated a serious discussion by the HMO as to whether OxyContin should be prior authorized. As you know, a restriction of this magnitude can ***greatly impact sales.***"²⁴⁷

152.2. Purdue's Phil Cramer replied to this email, stating that Purdue "must take a hard line in promoting OxyContin q12h...Q12-Q8-Q6-Q4 is no longer 'just' a matter of using the drug appropriately and effectively. **This issue is also critical to keep OxyContin available and reimbursible [sic] by MC plans and by PBM's!**"²⁴⁸

152.3. Similarly, in a July 25, 2001 sales training presentation titled "QxyContin q12h Workshop," promotion of OxyContin "as a true q12h drug" was needed to "differentiate OxyContin from MS Contin and other long-acting morphines," which are dosed Q8h or Q12h, otherwise "the rationale to keep [OxyContin] on hospital and MCO formularies is gone."²⁴⁹

152.4. In this same presentation, Purdue addressed "[w]hy is q12h so important," explaining:²⁵⁰

²⁴⁷ SHC-000006498 (emphasis added).

²⁴⁸ SHC-000006498 (emphasis added).

²⁴⁹ PPLP003996972 at 4.

²⁵⁰ PPLP003996972 at 1, 6.

Why is q12h Dosing So Important?

- Managed care companies are denying or will start denying shorter prescriptions
- Pharmacies may refuse to fill any Rx that is otherwise
- Increased FDA/DEA oversight
- Proper dosing minimizes diversion and abuse

152.5. Purdue also acknowledged in this presentation that prescribing OxyContin Q8h “is not malpractice” and would be “within the prescribing guidelines for titration”:²⁵¹

The Reality

- Although within the prescribing guidelines for titration, q8h is not within the recommended dosing guidelines.
- This is not malpractice, and we should never suggest that the physician could be held accountable for prescribing outside the package insert.
- Refocus the clinician back to q12h dosing with a complete explanation of the AcroContin™ delivery system and the importance of maintaining that dosing schedule.

153. Despite this, Purdue instructed its sales representatives to aggressively discourage healthcare providers from prescribing OxyContin on a less than Q12h basis and instead encourage them to increase the dose of OxyContin.

²⁵¹ PPLP003996972 at 10 (emphasis added).

153.1. In a July 18, 1999 document titled “What’s the OxyContin Message?” Purdue provided sales representatives a response to a doctor who “doesn’t believe it [OxyContin] works 12 hours,” stating that OxyContin Q12h was tested in “713 pts [patients] preNDA – Q12 at right dose is right dose.” This response failed to disclose the need for rescue dosing in the clinical trial.²⁵²

153.2. In a memo on January 20, 2000 distributed to the South Western Region sales representatives, the issue of Q12H versus Q8H was addressed. Sales representatives were told they “need to make sure that we are fighting the good fight for the patients, and sell OxyContin Q12H with conviction.” If doctors were prescribing OxyContin Q8h, the memo instructed sales representatives to “challenge [prescribers] to better assess their patients,” noting “the dose may not be high enough during the day.”²⁵³

153.3. In the July 25, 2001 sales training presentation discussed above, Purdue told sales representatives that “[t]his is an extremely important topic for the company right now. All managers and representatives must remember the **“BIG PICTURE”** when it comes to OxyContin. We cannot be afraid to address dosing other than Q12h with clinicians because we fear a drop in sales. It is imperative clinicians know where we, as a company, stand on this issue.”²⁵⁴

153.4. Similarly, in a Purdue sales training document titled “Q12h vs. Q8h Warfare,” sales representatives were told, “[t]he action of adding a dose, as opposed to increasing the Q12h dose, needs to be nipped in the bud. NOW!!.”²⁵⁵ They were further

²⁵² SHC-000008102 at 2.

²⁵³ PPLP003996839.

²⁵⁴ PPLP003996972 at 2.

²⁵⁵ PPLP003996830

advised that “the war is on – OxyContin is a true 12h product. Help the MD see that 12h is appropriate dosing for the patient controlling the pain, enhancing quality of life, even if it means using an escalating dosage and number tablets.”²⁵⁶

153.5. This sales training document encouraged sales representatives to focus physicians on titrating upwards the dose of OxyContin rather than changing the dosing frequency, commenting that increasing the dose would “result in a bigger bonus for us!!.”²⁵⁷

154. In accordance with Purdue’s directives, Purdue’s sales representatives discouraged healthcare providers from dosing OxyContin less than Q12h and encouraged them to instead increase the dose upwards.²⁵⁸

154.1. March 6, 1997 (West Virginia) - “HE IS 76% OXYCONTIN, BUT HE STIL IS DOSING IT Q8 FOR SOME PATIENTS, I EXPLAINED HOW THE CURVES WOULD OVER LAP AND OVER A PERIOD OF TIME ACCUMULATE. **I EXPLAINED IF IT WASN'T LASTING 12 HOURS, HE SHOULD IN- CREASE THE DOSE.** THE PAIN COULD HAVE INCREASED OR THEY COULD BE UNDER DOSED.”²⁵⁹

²⁵⁶ *Id.*

²⁵⁷ *Id.* (emphasis added).

²⁵⁸ Purdue was aware through early testing that prescribers were not dosing in accordance with package insert. In a January 4, 1994, Project Team Contact Report between Purdue and the FDA discussing “OC93-0704 – Package Insert Testing Study,” one of the results found was that “one half of the physicians did not dose according to the package insert.”²⁵⁸ The following year, Purdue learned that a one-time Purdue clinical investigator was conducting a study using Q8h. Rather than encourage the development of data on Q8h dosing, Robert Reder, M.D., Purdue’s Vice President, Medical Director sent a letter on July 24, 1995 to the clinical investigator, stating that “this situation concerns me as OxyContin has been developed for q12h dosing only (see draft package insert). In order to develop accurate information on alternative dosing schemes, proper controlled studies would need to be conducted. Because such studies have not yet been performed, I request that you not use a q8h dosing regimen.” SHC-000007900

²⁵⁹ PKY182404281 (emphasis added).

154.2. May 12, 1997 (New Jersey) - **PTS MOSTLY ON 20 Q8** SHE'S EASY TO TALK TO AND I ASKED IF THAT'S THE DOSE HOW DO YOU TITRATE OH SOMETIMES JUST ADD ANOTHER PILL AT NIGHT OR IN AM, **THIS IS EASIEST WAY INCREASE DOSE AT Q12 DON'T SHORTEN TIME** THEN INCREASE BY 50% EVERY 24 HRS WHEN STABLE MOVE TO NEXT TAB SIZE²⁶⁰

154.3. August 4, 1998 (New Jersey) - "A SLEW OF PROBLEMS W/ OXY FROM **NOT LASTING 12 HRS** TO SEVERE CONSTIPATION, AFTER A SERIES OF? HE'S NOT DOSING HIGH ENOUGH AT Q12 AND THEY DON'T START A LAXATIVE UNTIL PT IS CONSTIPADNEXT START AT BASICS"²⁶¹

154.4. February 22, 1999 (Ohio) - "PATIENT AT PHARM IN DAYTON HAVING PROBLEMS-**40MG Q8HR SHE BELIEVES THE PATIENT**"²⁶²

154.5. March 30, 2000 (West Virginia) - "**sd oxy is not lasting 12 hrs. dr dosing 20 q12. pted out needs to increase a little hihger and use the 10 mg tabs.** dr sd also has a lot of chronic pain pts. usually uses ultram tyl 3 or hydrocet. gave and disc caldwell and reminded of dosing convenience lower se's as demonstrated in paper. ncp: chronic pain .. lower abuse pot"²⁶³

154.6. November 13, 2001 (New Jersey) - "Vidaver starts everyone **on q12h and then when needs to titrate he puts them on q8h so he doesn't have to write for 2 different strengths**. I went over 3-2 rule in order to avoid this and keep pt. on q12h. Dr.

²⁶⁰ PKY182317787 (emphasis added).

²⁶¹ PKY182331401 (emphasis added).

²⁶² PKY182144588 (emphasis added).

²⁶³ PKY182418949 (emphasis added).

Haliczer - is putting most everyone on q8h No breakthru neither is Vidaver They believe pts have too much problem w/ IR meds and goal of long-acting is to avoid addictive potential w/ popping pills all day. and w/o breakthru pts. are saying it's not lasting long enough"²⁶⁴

154.7. July 15, 2002 (New Jersey) - "**Polcer said writes some Q12 and some Q8 said its not always lasting 12 hours** went over indication and package insert and titration Went over the PPI said it will be helpful but too much info for pt sometimes confuses them or leads them to believe they are having side effects that they aren't really having I pointed out that the PPI has bold print of to be swallowed whole"²⁶⁵

154.8. May 19, 2010 (Ohio) - You went in with the goal of finding out how she utilizes her short-acting opioids. **You never got to this as she began telling you about a patient taking 80mg q12h that is not lasting 12 hrs. and how she is supplementing with OxyContin 20mg two hours after the 80mg dose.** You explained to her that OxyContin is only indicated for q12h dosing and there is no data to support anything other than this dosing. You handled this correctly.²⁶⁶

155. In my opinion, Purdue developed a strategy to increase the total daily OxyContin dose but failed to inform the public and put patients at risk in response to OxyContin not being effective for 12 hours.

3. Purdue Overstated the Benefits of OxyContin with Respect to Sleep, Work, and Physical Activity and Leisure

156. Prior to the approval of OxyContin, Purdue submitted OxyContin promotional launch materials for FDA review. These materials included claims that OxyContin improved a

²⁶⁴ PKY182212989 (emphasis added).

²⁶⁵ PKY182178532 (emphasis added).

²⁶⁶ PPLPMDL0020000002 (emphasis added).

patient's quality of life; specifically, that "patients reported that OxyContin did not impair their ability to...sleep, walk, perform normal work, enjoy life, get along with other people."²⁶⁷

157. While substantial evidence existed to support these quality life claims when comparing OxyContin to placebo, Purdue lacked evidence to support these quality of life claims as compared to other opioid products, which FDA noted on January 31, 1996 stating that "this claim would be misleading because it fails to disclose that these improvements were in comparison to placebo only."²⁶⁸

158. In response, Purdue corrected its promotional materials on February 9, 1996 to highlight that its quality of life claims for OxyContin were "relative to placebo."²⁶⁹

159. Nonetheless, in sales training and promotional materials, Purdue did not tell healthcare providers that OxyContin resulted in an improved quality of life *as compared to placebo*—a claim it lacked substantial evidence to make.

159.1. For instance, in a November 4, 1996 memo from Training and Development to the Entire Field Force on planning an effective sales presentation, Purdue's Jim Lang recommended that sales representatives tell doctors that "OxyContin can provide pain relief to your patients, allowing them to sleep through the night, while potentially creating less chances for addiction than immediate-release opioids."²⁷⁰

²⁶⁷ PURCHI-000622714 at 13. On a January 11, 1996, Purdue resubmitted promotional materials to FDA that revised the quality of life claims, stating "OxyContin 20 mg q12h...significantly decreased pain, improved quality of life, mood and sleep." PURCHI-000622986.

²⁶⁸ PURCHI-000623100 at 1-2.

²⁶⁹ PURCHI-000623112 at 7, 20, 43 (emphasis added).

²⁷⁰ SHC-000003754 at p. 2.

159.2. In addition, in January 2000 training materials, Purdue provided sales representatives a pamphlet that described OxyContin as “[i]mprov[ing] quality of life, mood, and sleep.”²⁷¹

159.3. In 2001, a second version of a promotional video entitled, “I Got My Life Back: Patients in Pain Tell Their Story,” Purdue presented stories of patients who had taken OxyContin and included unsubstantiated quality of life claims.²⁷²

160. Purdue’s sales representatives proceeded to tell healthcare providers that OxyContin was proven to improve a patient’s quality of life as compared to other opioid products without substantial evidence:

160.1. March 4, 1996 (Ohio) - HUGE PERCO WRITER, **POSITIONED AGAINST Q4H DRUGS AND QUALITY OF LIFE**, WAS UNCERTAIN REGARDING STARTING DOSES, SHOWED EQUI DOSES CERTAIN PATIENTS.²⁷³

160.2. July 10, 1996 (Ohio) - WORKING W PAM TO GET MORE PAT'S CONVERTED. **THEY USE ALOT OF PERC AND THERE IS NO REASON FOR NOT USING. SLEEP AND QUALITY OF LIFE ARE IMPORTANT ISSUES AND SHOULD BE FOCUSED UPON.**²⁷⁴

160.3. September 9, 1996 (Ohio) - SHOWED OXY VISUAL. STRESSED FAST ONSET, BETTER COMPLIANCE AND LESS ABUSE THAN COMBOS THEY ARE USING WILL TRY. **QUALITY OF LIFE AND SLEEP** NT.²⁷⁵

²⁷¹ PKY180261022 at 6.

²⁷² U.S. Government Accountability Office, *Prescription Drugs: Oxycontin Abuse and Diversion and Efforts to Address the Problem*, GAO-04-110 (Washington, DC, December 2003) at 32-33.

²⁷³ PPLPMDL0080000001 (emphasis added).

²⁷⁴ PPLPMDL0080000001 (emphasis added).

²⁷⁵ PPLPMDL0080000001 (emphasis added).

160.4. January 29, 1997 (Ohio) - T2 DR.CORTESE HE WAS CONCERNED WITH THE COSTS.OF OXY. HE SAID THAT HE STARTS WITH VICODIN,THEN TO PERCOCET,AND THEN TO OXY OR MS-CONTIN OR ... NTXC:MENTION HOW EXPENSIVE DURAGES IS IN COMPARISON TO EVERYTHING ELSE PUSH OXY ON ALL FORMULAR AND MEDICAID, **ALSO STRESS PT QUALITY OF LIFE**. Q12H DOSING VS Q4-6H DOSING USE START W/STAY W/AND GAIN EARLIER USE **VS.COMBOS**.²⁷⁶

160.5. February 5, 1997 (Ohio) - TD2 DR.ABOUT CESSATION OF THERAPY AND HE SAID THAT SOME OF THOSE PTS.REQUEST CERTAIN PRODUCTS.I ALSO SHOWED OSA STUDY IN PI AND 18 MONTH STUDY FOR OA PTS.I TALKED TO ABOUT COMBOS NTXC:BE MORE SPECIFIC ON THE PT TYPE TO **LOOK FOR VICODEN, T3, OR PERCOCET PTS AND CLOSE WITH QUALITY OF LIFE FOR THE PT**.ON Q12H DOSING VS.Q-4-6DOSING& COVER INS.COVERAGES&COSTS.²⁷⁷

160.6. February 6, 1997 (Ohio) - TD2 DR.GILBERT HE SAID THAT HE WOULD TRY OXY ON A FEW PTS. TO SEE HOW IT WORKS. HE LIKED THE FACT OF NO APAP OR ASA & LONG ACTION VS. SHORT ACTION AND CESSATION OF THERAPY.WE TD' ABOUT UNI AND COPD PTS.NOCTURNAL SYMPTOMS AND ASKED FOR NEW UNI STARTS NTXC:ASK IF HE HAS STARTED ANY NEW PTS.ON OXY & **REPOSTION IT INPLACE OF COMBO'S AND PT QUALITY OF LIFE INCR.**²⁷⁸

²⁷⁶ PPLPMDL0080000001 (emphasis added).

²⁷⁷ PPLPMDL0080000001 (emphasis added).

²⁷⁸ PPLPMDL0080000001 (emphasis added).

160.7. September 30, 1997 (Ohio) - WENT OVER SUNSHINE POST OP STUDY. USING DARVOCET, VICODIN PERCOCET. HIT DELIVERY SYSTEM, IMPROVED QUALITY OF LIFE. FOLLOW UP WITH Q12 DOSING.²⁷⁹

160.8. February 12, 1998 (Ohio) - DR SEES ALOT OF GERIATRIC PATIENTS, AND COPD PATIENTS.HIT OXYCONTIN NOMALIGNANT USE, USED PI TO SHOW CONVERSIONFACTORS OF HYDROCODONE AND OXY. PI FOR LESS FREQUENT DOSIG AND IMPROVE QUALITY OF LIFE.UNI, HIT QD WITH IMPROVED PULM FUNCTION PEAKING IN THE AM.²⁸⁰

160.9. April 15, 1998 (Ohio) - DR USES PERCODAN, HIT OXY WITH DELIVERY SYSTEM, LESS FREQUET DOSING, IDEA OF IMPROVEMENT IN QUALITY OF LIFE, NOT TOTAL PAIN CONTROL. QUICK ONSET OF ACTION WITH Q12 DOSING.²⁸¹

160.10. August 6, 1998 (Ohio) - “OXY FOR ALL VIC PTS/LESS ABUSE POTENTIAL AND PTS CAN SLEEP THROUGH PM.”²⁸²

160.11. January 5, 2000 (Ohio) - Advantage of using Oxy vs Percocet for chronic pain, quality of life issues. B.O./ Sit-down call. Seems to have Oxy niched on third step, after NSAIDS & short-acting combos. Discussed Oxy as one to “Start/stay with”. No need to go to combos, patients then has to clock watch. With Oxy, prevent

²⁷⁹ PPLPMDL0080000001 (emphasis added).

²⁸⁰ PPLPMDL0080000001 (emphasis added).

²⁸¹ PPLPMDL0080000001 (emphasis added).

²⁸² PPLPMDL0030008507 at 1 (emphasis added).

rather than manage pain. 12 hour smooth blood levels for A-T-C pain control. Oxy Wall conversion chart & titration guide.²⁸³

160.12. March 1, 2000 (Ohio) - Pain the 5th Vital sign, page 16. Stay on recommendation of long-acting opioids. Inquired about patients he has known for a long time, trusts. Those are the patients that would be excellent candidates for Oxy. **The elderly patient who has been taking T-3, hydrocodone, darvocet etc. Quality of life issues for them....sleep thru the night, rested during the day.**²⁸⁴

160.13. October 16, 2000 (Ohio) - **introduced oxy for use in place of short acting** usually t-3 or vicodin discussed side effects and dosing use po5 c-asked forrx **discussed quality of life** and better pain control senokot for side effects c-asked for rx.²⁸⁵

160.14. December 4, 2001 (Ohio) - gave linda titration pamphlet **focusing on quality of life with long acting vs short acting agent** when pt fits indication for oxycontin POA: need to share aps guidelines re short acting agents when linda has more time.²⁸⁶

160.15. April 30, 2003 (Ohio) - lecture dinner--explained oxycontin q12h, **dr clinton had talked about quality of life, so I mentioned keeping highest quality with q12h dosing,** titration every 1-2 days. also remind senokot. need to take CE brochures to fellows room and new titration g lecture dinner....²⁸⁷

²⁸³ PPLPMDL0080000001 (emphasis added).

²⁸⁴ PPLPMDL0080000001 (emphasis added).

²⁸⁵ PPLPMDL0080000001 (emphasis added).

²⁸⁶ PPLPMDL0080000001 (emphasis added).

²⁸⁷ PPLPMDL0080000001 (emphasis added).

160.16. July 30, 2007 (Ohio) - “discussed use of low-dose Oxycontin & where it fits w/ patients in his practice. Tied together use of assessment guide w/ low-dose 10mg to reduce pain & improve functionality. Doc said he has a couple of patients who could benefit from this”²⁸⁸

161. In addition, Purdue’s key opinion leaders gave presentations and otherwise conveyed that OxyContin improved patients’ quality of life without clarifying that this claim was valid only as compared to placebo.²⁸⁹

162. Likewise, Partners Against Pain, Purdue’s pain advocacy organization, claimed that opioids improved a patient’s quality of life without stating that this comparison was only valid as to placebo only.²⁹⁰

163. In my opinion, Purdue overstated the benefits of OxyContin with respect to sleep, work, and physical activity/leisure.

4. Purdue Promoted OxyContin for Indications that Were Broader than Supported by Substantial Evidence and for Which Safety and Efficacy Were Not Established

164. OxyContin has never been expressly approved for the use in osteoarthritic pain, lower back pain, or post-operative pain nor has OxyContin been approved for the use of all pain or even mild pain.²⁹¹

²⁸⁸ PPLPMDL0020000001 (emphasis added).

²⁸⁹ PDD1501606099 at 40; *see also* PDD8801245481 (list of paid Purdue speakers).

²⁹⁰ SHC-000024493 at 5 (“Pain-free patients are a help, not a hindrance to the treatment of the primary disease. With pain under effective control patients enjoy a better quality of life. They can eat, sleep, perform daily activities more normally.”) Purdue also supported pain advocacy organizations that downplayed these risks. *See* Section XI.

²⁹¹ *See* Section XI.

165. The initial OxyContin label referenced in the Clinical Trial section three non-malignant pain studies—one involving osteoarthritis pain, another involving lower back pain, and a third post-operative study.

166. The inclusion of these non-malignant pain studies in the OxyContin label was described by Purdue in a 1996 Purdue Research Center report as “so valuable”²⁹² with Purdue noting “our package insert team ... did its job skillfully” because the OxyContin label “contain[ed] all the major elements of our long-range marketing platform for [OxyContin]” despite FDA’s Curtis Wright stating “that all of this promotional material would disappear.”²⁹³

167. Despite the references to the non-malignant pain studies in the package insert, FDA told Purdue on multiple occasions that OxyContin should not be used in these patient populations.

167.1. In a March 19, 1993 teleconference, FDA Medical Reviewer, Dr. Curtis Wright, told Purdue that “there were very strong opinions of members at the FDA that opiates should not be used for non-malignant pain,”²⁹⁴ a labeling claim for osteoarthritis would be “strongly resisted,” and that long-term use in osteoarthritic patients was believed to be “unwarranted” by individuals at FDA.²⁹⁵

I met with Dr. Wright to discuss the osteoarthritis protocols OC 92-1102 and OC 92-1103. Dr. Wright provided me with some information on Oxaprozin (attached) to show the pitfalls of OA studies. Dr. Wright had both general and specific comments on the protocols. **Of greatest**

²⁹² PKY180673220 at 10.

²⁹³ PKY180673220 at 3.

²⁹⁴ PPLP004030167 at 11.

²⁹⁵ SHC-000002018 at 1. With respect to Purdue’s decision to study OxyContin in osteoarthritis patients (clinical study OC 92-1102), Dr. Wright recommended that Purdue “rewrite the introduction to OC 92-1102 to make it clear that osteoarthritis is being used as a pain model and that Purdue Frederick recognizes single-entity opiate use is not appropriate except in highly selected subpopulations.” *Id.*

importance is the fact Dr. Wright said that for certain individuals in the division and in the agency, the use (i.e., long term) in osteoarthritis is unwarranted. The way the protocols are written, it looks as if Purdue Frederick is attempting to obtain labeling claims for pain from osteoarthritis. This will be strongly resisted. He suggested that we chop the extension protocol (OC 92-1103) and rewrite the introduction to OC 92-1102 to make it clear that osteoarthritis is being used as a pain model and that **Purdue Frederick recognizes single-entity opiate use is not appropriate except in highly selected subpopulations.** If we wish to perform a long-term study in osteoarthritis patients, **we should study highly selected patients. Such as study should include questionnaires and data collection directed toward abuse, evaluation of diversion,** increase use with time (tolerance), efficacy and safety. Clinicians as well patients as well as patients must be questioned.²⁹⁶

167.2. In the FDA's Medical Officer Review of OxyContin from May 3, 1995, the FDA Medical Officer confirmed that Purdue did not have the data to support use in osteoarthritis patients, stating "this data is not adequate by itself to support an OA indication, but [OC 92-1102] is a very helpful trial in a non-oncologic chronic pain model."

167.3. Similarly, a review by the FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) of OxyContin promotional materials in December of 1995 resulted in FDA stating that it would not be appropriate for Purdue to reference results the clinical study in post-operative pain patients. In a letter to Purdue, DDMAC wrote that "by referencing this one single-dose study in post-operative patients, it implies that OxyContin is indicated for this patient population." DDMAC recommended that if Purdue wished to use this study "the introduction be qualified by prominently including the statement from the approved product labeling, 'OxyContin is

²⁹⁶*Id.* (emphasis added)..

not recommended...for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery).’’²⁹⁷

167.4. In 2001, FDA repeated the same concerns it had raised in 1995 that OxyContin should not be used in post-operative treatment, for osteoarthritic pain, or for intermittent pain treatment.²⁹⁸

167.5. In addition, on January 17, 2003, FDA’s Division of Drug Marketing, Advertising, and Communications (DDMAC) issued a warning letter to Purdue regarding off-label promotion for a broader range of patients than indicated:

Your advertisements suggest that OxyContin can be used in a much broader range of pain patients than has been proven to be safe and effective. This is even more problematic from a public health perspective given the serious safety risks associated with the drug and the serious deficiencies in the safety information presented in your advertisements.

The only indication information presented in the body of the advertisements (indeed, the only information from the boxed warning included at all as part of the body of these advertisements) is the partial language from the Indications and Usage section of the PI, “For moderate to severe pain when a continuous, around-the-clock analgesic is needed

²⁹⁷ PURCHI-000622957 at 12.

²⁹⁸ PURCHI-000679976 at 4. FDA noted that OxyContin’s indication as provided in the label was “broad and may not adequately reflect the intended population”:

She initiated a discussion regarding the drug’s intended indication by asking who the proper population is for this type of drug product. The indication of “moderate to severe pain for patients who need to be on opiates for more than a few days” is broad and may not adequately reflect the intended population. The label should clearly state that this drug product should only be used in patients who require opiates for an extended period of time, that it should not be utilized for first-time treatment of pain, and that it is not for intermittent use. She further stated that a black box warning for overdose, abuse and death may be appropriate. Dr. McCormick commented on the studies in the clinical trial section of the label. There are equivalence and open-label studies that are conducted in artificial settings. The arthritis study enrolled patients on non-steroidal and anti-inflammatory agents or IR opiates, for whom OxyContin may not have been the next logical step in pain management. Furthermore, post-operative and ambulatory surgery settings may not be appropriate uses for OxyContin. Dr. Jenkins summarized by saying that the label will need a major overhaul.

Id.

for an extended period of time,” which you present by itself at the top of these advertisements ... These presentations are insufficient to give appropriate context and balance to your claims broadly promoting the use of this drug for pain relief ... Therefore your advertisements fail to adequately communicate the actual indication for OxyContin and suggest its use for pain relief in a much broader range of patients than indicated.

In addition, your advertisements fail to present in the body of the advertisements the other important limitations on the indicated use of OxyContin as noted above...The body of the advertisements, however, fails to present the important limitations on the use of OxyContin restricting it to certain hospitalized patients, as described in the OxyContin Pl... You fail to present in the body of your advertisements any of these important limitations, thus suggesting the use of OxyContin in inappropriate patients.²⁹⁹

168. Before and after FDA’s comments regarding off-label use, Purdue instructed its sales force to “aggressively position OxyContin for use in osteoarthritis, low back pain, post neuropathic neuralgia and post-surgical applications, where appropriate.”³⁰⁰

169. According to sales call notes maintained by Purdue, the sales force promoted and encouraged the use of OxyContin for the treatment osteoarthritis and post-operative pain among other off-label indications, such as for milder pain, short term pain, for “all pain,”³⁰¹ lower back pain, headaches and sprains, which are widely regarded as inappropriate for treatment by a strong opioid product like OxyContin:

²⁹⁹ PKY181392830 at 5-6. Purdue disagreed with FDA’s characterization, stating “[t]he ads do not recommend usage of OxyContin beyond the FDA-approved label indication.” SHC-000008196 at 2. However, Purdue’s internal call notes indicate that its sales force continued to promote for off-label uses. See PPLP004032436, PKY182144233, PKY182139597, PKY182145546, PKY182140361, PKY182141419, PKY181917492, PKY181917494, PKY181917498, PPLPMDL0030008507, PPLPMDL0030011819, PKY182156626, PPLPMDL0020000002.

³⁰⁰ SHC-000008166. Further, in an internal Purdue document listing “OXYCONTIN SELLING POINTS,” one selling point was that OxyContin is “[n]ot contraindicated for the treatment of acute and post-op pain,” suggesting that OxyContin can in fact be used safely in those situations. SHC-000008153 at 2

³⁰¹ See PPLP004032436 at 64.

169.1. May 23, 1997 (Kentucky) - “NT: USE APS BOOK TO SHOW THAT
OXY APPROPRIATE FOR MILD PAIN THROUGH SEVERE PAIN.”³⁰²

169.2. September 10, 1997 (Ohio) - “**DID COME UP WITH OA AND BACK
PAIN PT FOR USE**, WENT OVR DIF FROM VIC, AND DEFINED CHRONIC USE,
SD WILL USE, FINALLY SD OK TO OXY”³⁰³

169.3. February 9, 1998 (Ohio) - “**LOOKED AT BACK PAIN AGAIN, SD I
NEED NOT WORRY HE USES AS MUCH OXY AS HE CAN**, BUT THEN
AGREED PROBABLY SOME PTCOULD GET MORE RELIEF FROM OXY VS
MAJOR NSAID USE, SD WILL TAKE A LOOK AT THESE PT WHENCOME IN”³⁰⁴

169.4. April 24, 1998 (Ohio) - “**OXY FOR ALL PTS POST OP**/FILE
CARD/POINTED OUT AGAIN HOW TO DOSE/TITRATE/BENEFITS HUGE OVER
SHORT ACT DRUGS/Q12 HR DOSE, NO TYLENOL/LESS ABUSE POTENTIAL.”³⁰⁵

169.5. September 17, 1998 (Ohio) - “FILE WITH BACK PROFILE AND **HOW
THE PI SUPPORTS THE USE STUDY OA, LOW BACK AND POST OP**, LESS
ABUSE POTENTIAL TOO”³⁰⁶

169.6. August 22, 2000 (Ohio) - “TRYING NEW APPROACH TO MD **WILL
SUPPLY WITH MANY MANY STUDIES RE: USES OF OXY IN MANY
DIFFERENT WAYS (I.E. ASYMETRIC IN OSTEOARTHRITIS) TO TRY TO
INCREASE USAGE OF OXY** -THOUGHT BEHIND THIS IF MD THINKS THAT IT

³⁰² PPLP004032436 at 21 (emphasis added).

³⁰³ PKY182144233 (emphasis added).

³⁰⁴ PKY182145546 (emphasis added).

³⁰⁵ PKY182140361 (emphasis added).

³⁰⁶ PKY182141419 (emphasis added).

IS HIS DECISION TO CHANGE HE IS MORE LIKELY TO FOLLOW THROUGH
DECISION; CONTINUE TO SUPPLY HIM WITH INFO RE: OXY AND NEW 160
MG”³⁰⁷

169.7. December 12, 2000 (Ohio) - “**OXY IN OSTEOARTHRITIS STUDY
BY CALDWELL HANDED TO MD** ALONG WITH OXY IR FILE”³⁰⁸

169.8. August 27, 2008 (Ohio) – “He gained information from the physician
about the type of disease states he most likely treats. Dr. said cancer and back pain. **He
asked the physician to prescribe OxyContin instead of short-acting opioid.**”³⁰⁹

169.9. October 27, 2008 (Ohio) – “This was a good call. Dr. started off by
saying he tries not to prescribe OxyContin. **Tom asked probed the Dr. for his
hydrocodone use and pointed out the benefits of low dose OxyContin instead of
hydrocodone/APAP for his low back pain patients.** Dr. said this is what he sees most
of. Tom got the physician to commit to using the 10mg and the benefit the physician saw
was no APAP.”³¹⁰

169.10. February 11, 2010 (Ohio) – “**Nice job getting him to think about
conditions in which he would initiate OxyContin (arthritis, and documented low
back pain).** You had a chance to update him with the Medicaid changes.”³¹¹

170. In my opinion, Purdue promoted OxyContin for indications that were broader
than supported by substantial evidence and for which safety and efficacy were not established.

³⁰⁷ PPLPMDL0030008285 (emphasis added).

³⁰⁸ PPLPMDL0030008285 (emphasis added).

³⁰⁹ PPLPMDL0020000002 (emphasis added).

³¹⁰ PPLPMDL0020000002 (emphasis added).

³¹¹ PPLPMDL0020000002 (emphasis added).

D. Despite Ongoing and Increasing Evidence of OxyContin Abuse, Purdue Failed to Take Reasonable Steps to Correct its Prior Misleading Statements Regarding the Safety of OxyContin and Opioids in General

1. Purdue's Promotion and Sales of OxyContin Increased as Reports of Abuse Grew

171. In the first five years of Purdue's promotion of OxyContin, Purdue increased its marketing expenditures by over 1,300% with sales increasing from less than \$50 million in 1996 to over \$1.08 billion by 2000.³¹² As Purdue acknowledged in 2001, its promotional activities "contributed to a paradigm shift,"³¹³ which expanded the use of opioids in treating pain.³¹⁴

172. As prescriptions and sales of OxyContin increased, Purdue acknowledged that it was anticipating increased reports of abuse and addiction. In an email exchange that began in July 1999, Purdue employees discussed a nurse who was planning to publish a clinical report that highlights OxyContin as a drug of abuse. Robert Reder responded on August 1, 1999 that "this type of report is one which we had been anticipating as the use of OxyContin grow... We have had reports of abuse of OxyContin both through our spontaneous reporting system and through the internet watch set up by Mark [Alfonso]."³¹⁵

³¹² Compare 1998 Budget Plan OxyContin, at PP00123 at 42 with 2002 OxyContin Budget Plan, SHC-000001228 at 58.

³¹³ PDD1503491667 at 1; see also PPLP003409951, PPLP003541889, PPLP004001344.

³¹⁴ In Purdue meeting minutes from an April 23, 2001 meeting between Purdue and the FDA, Purdue agreed that there had been a "shift in prescribing patterns" from malignant to non-malignant pain conditions, including a ten-fold increase in OxyContin prescriptions as compared to extended-release morphine:

It was noted, from 1995 to present there had been a shift in prescribing patterns out of oncology specialties into family practitioners and, when looking by indication, mentions of neoplasm were decreasing and musculoskeletal disease were increasing. Musculoskeletal disease included such terms as lumbago, myalgia and other back pain related terms. Dr. Pollock compared the number of mentions in IMS of OxyContin to MS Contin and noticed that while MS Contin prescribing had remained relatively constant, OxyContin had increased 10 fold. The Agency implied that this was a trend they were concerned with. Mr. Friedman noted that these observations were consistent with our understanding of the data we have seen.

PURCHI-000675080 at 2.

³¹⁵ PKY180233315 at p. 1.

173. In as early as 1997, Purdue's sales force documented reports of addiction and abuse from OxyContin with reports increasing over time,³¹⁶ and by September 29, 2000, Purdue executives had been notified of "abuse of epidemic proportions" as detailed in an email from an internist in Virginia, Dr. Art Van Zee.³¹⁷ In his response to Dr. Van Zee, Purdue's Medical Director, Dr. Haddox, noted to his colleagues that he had not committed to any particular course of action: "I have responded to this email, as well as talking to him personally. I indicated that we were seriously considering his concerns, without committing to any specific course of action."³¹⁸

³¹⁶ See Schedule 11.

³¹⁷ Email from Van Zee to Haddox, Sept. 27, 2000, PKY180296112 at 2 in which Dr. Van Zee stated:

We are seeing oxycontin abuse of epidemic proportions in southwest Virginia. As a primary care general internist in Lee County, Virginia for the last 24 years I have been seeing a very small number of narcotic dependent patients (eg. 1-3 patients per year) in an otherwise busy general internal medicine practice. This started to change about 1-2 years ago when we started seeing increasing numbers of patients that had been abusing oxycontin and had become addicted. The oxycontin is being snorted or IV injected. Most addicts are young, late teen years to their thirties, both men and women. All medical providers in the area are seeing frequently overdoses (some fatal), abscesses, and infections, Hepatitis C, and occasional bacterial endocarditis related to intravenous drug abuse. The expected wave of more Hepatitis C and HIV in the population is sure to follow. The medical, personal, and social costs are extra-ordinary in the poor rural area with few resources to deal with the problems we are facing. There has been an enormous rate of increase in the crime rate which is drug related. In a nearby Tazewell County, the Commonwealth Attorney Dennis Lee has noted that 70% of serious crimes in Tazewell County are now drug related crimes. Our Commonwealth Attorney in Lee County has estimated to me that about "90 percent" of the serious crimes here are drug related. Not a week goes by that I'm not talking with parents about their young adult children that are losing their jobs, spouses, children, and homes to this addiction. Equally frightening to me is that-on a recent county-wide survey in the Lee County School System, 10% of our 7th graders and 20% of our 12th graders have used oxycontin.

Dr. Van Zee urged Purdue to make changes to its marketing:

I think that the whole marketing/advertising approach for Oxycontin needs to be discarded. I think you can understand that the giving of gifts like a beech hat with "Oxycontin" on it, or a CD "Swing is Alive" "Swing in the right direction with Oxycontin"--in light of the medical/personal/social/societal problems related to Oxycontin is way beyond the bounds of distasteful.

Id. In response, Purdue's Dr. Udell agreed, stating "[a]s you know, I agree with Van Zee's criticism of this type of promotional materials." *Id.* at 1.

³¹⁸ PDD8801179978 at 1.

174. In addition, Purdue took steps to minimize negative attention regarding the abuse of OxyContin by focusing on the under-treatment of pain.

174.1. For instance, beginning in 1999, Purdue used public relations firms to monitor local and national news media, state and federal legislatures, advocacy groups, research programs, etc. for “issues/topics in the pain management area that could potentially pose a threat to Purdue Pharma or its products.”³¹⁹

174.2. These firms provided crisis management to Purdue for multiple purposes, including counteracting negative media attention related to the abuse and addiction of OxyContin by “getting information on the patient’s side of the story to reporters.”³²⁰

175. Purdue’s Marketing Department also worked to publish stories that “focus[ed] more on telling the pain management story”³²¹ with Purdue’s Dr. Richard Sackler remarking that “we will have to mobilize the millions that have serious pain and need our product” in the face of negative media attention.³²²

2. FDA Advised Purdue that it Needed to Correct Misinformation Regarding Opioids through a Risk Management Plan and Limit the Expanded Use of Opioids

176. Following increasing reports of abuse, addiction, and diversion,³²³ FDA identified the need for an OxyContin risk management plan in 2001,³²⁴ requesting that Purdue develop

³¹⁹ PKY183037000; *see also* PPLPC045000005939.

³²⁰ PPLPC045000005939; *see also* PPLPC029000036245.

³²¹ PDD1706196246.

³²² PDD8801133516; *see also* PDD1501720041.

³²³ On April 23, 2001, a meeting was held among representatives of Purdue and FDA. FDA’s “Dr. McCormick made opening comments. She stated that the Agency is taking the recent upsurge of prescription drug abuse, and specifically, OxyContin abuse and diversion, very seriously.” PURCHI-000679976 at 3. Citing IMS data, FDA identified one source of the problem being the change in prescribers and patient population, stating that “there has been a shift in primary prescriber-type for OxyContin from 1995 to 2000 from oncologist to family practitioners. The primary indication for which OxyContin is prescribed has also shifted from neoplastic to musculoskeletal disease.” *Id.* The FDA further identified OxyContin’s indication of ‘moderate to severe pain for patients who needs

such a program to include Purdue's advertising of OxyContin.³²⁵ FDA's Dr. Cynthia McCormick stated that she "considers the advertising [of OxyContin] as part of an overall Risk Management Program (RMP) that she sees occurring in two parts":³²⁶

176.1. The first part enunciated by FDA was with respect to prevention, calling for "[c]learer labeling which displays the risk and critical safety messages in a box warning, strengthened warnings about the abuse potential of the product and clarity about the appropriate indication for the product;" "issuance of a Dear Healthcare Provider Letter to alert practicing physicians to the changes in the label;" "retraining of Drug Detail Staff to the key messages of the RMP and the new label;" and "outreach education programs to bring the OxyContin safety message to communities (pharmacies and health care providers) that would be prescribing the product, through outreach educational programs, speakers bureau, CME opportunities and other mechanisms."³²⁷

176.2. The second part to this plan, identified by FDA was "Surveillance, Monitoring and Feedback." Specifically, the FDA stated that "the purpose of surveillance and monitoring is to assess the effectiveness of the prevention and educational part of the

to be on opiates for more than a few days' as being "broad and may not adequately reflect the intended population. The FDA stated that "the label should clearly state that this drug product should only be used in patients who require opiates for an extended period of time, that it should not be utilized for first-time treatment of pain, and that it is not for intermittent use" and that "post-operative and ambulatory surgery settings may not be appropriate uses for OxyContin." *Id.* at 4.

³²⁴ PURCHI-000679976 at 9. Specifically, FDA's Dr. Abrams "suggested an educational campaign to both consumers and practitioners and a national sampling and survey of physicians, inquiring about their perception of the sales representative message and their understanding of the drug and its appropriate uses." *Id.* at 6. FDA's Dr. McCormick "stressed the need for a prospective monitoring program that includes a risk management plan with measurable outcomes." *Id.* at 9.

³²⁵ *Id.*; PURCHI-000551125 at 3.

³²⁶ PURCHI-000551125 at 3.

³²⁷ *Id.*; PURCHI-000551125 at 4.

RMP in curtailing abuse and diversion and to trigger intervention when problems are discovered.”³²⁸

177. On August 3, 2001, Purdue submitted to FDA a proposed Risk Management Program (“RiskMap”) for OxyContin.

177.1. According to Purdue, “[t]he primary goals of this risk management plan are prevention through appropriate labeling and promotion of OxyContin Tablets, and appropriate interventions when significant abuse has occurred or significant risk for abuse has been identified.”³²⁹

177.2. As part of the RiskMAP, Purdue outlined several key messages to be communicated to healthcare providers: “OxyContin is NOT intended for use as a pain analgesic;” “OxyContin is not indicated for pain in the immediate postoperative period (for the first 12 to 24 hours following surgery), or if the pain is mild or is not expected to persist for an extended period of time;” and “OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.”³³⁰

177.3. The RiskMAP also identified how Purdue would disseminate those messages to healthcare providers, including Dear Doctor letters; accredited physician, nursing, and pharmacist continuing education programs; symposia at national/regional organization/society meetings; seminars; monographs; journal supplement; and promotional activities.

3. Despite FDA’s Warnings Regarding the Impact of Misinformation Concerning Opioids, Purdue Failed to Take Reasonable Steps to

³²⁸ *Id.*; PURCHI-000551125 at 5.

³²⁹ PDD8013007919 at 8.

³³⁰ PDD8013007919 at 9-10.

Correct its Misleading Statements and Continued to Expand the Opioid Market

178. Purdue submitted its proposed RiskMAP on August 3, 2001,³³¹ and contrary to the stated goal of this RiskMAP program, many of Purdue's communications with healthcare provider encouraged the use of OxyContin in manners inconsistent with the approved drug label and the spirit of the risk minimization plan requested by FDA.

178.1. For example, in a pamphlet for doctors, Providing Relief, Preventing Abuse: A Reference Guide to Controlled Substance Prescribing Practices, Purdue told healthcare professionals that addiction "is not caused by drugs." Instead, Purdue told doctors that addiction only occurs when the wrong patients get drugs and abuses them: "it is triggered in a susceptible individual by exposure to drugs, most commonly through abuse."³³²

178.2. Another Purdue publication, the Resource Guide for People with Pain, falsely assured patients and healthcare professionals that opioids are not addictive: "Many people living with pain and even some healthcare providers believe that opioid medications are addictive. The truth is that when properly prescribed by a healthcare professional and taken as directed, these medications give relief –not a 'high.'"³³³

178.3. In addition, Purdue distributed materials published by pain advocacy organizations supported by Purdue that contained false and misleading statements regarding the safety of opioids. For example, Purdue distributed 195,000 copies of guidelines published by the Purdue-funded Federation of State Medical Boards, which included the following misleading statement: "Pseudoaddiction: Pattern of drug-seeking

³³¹ PDD8013007919.

³³² PDD8013350426 at 12.

³³³ PPLP003325237 at 14.

behavior of pain patients who are receiving inadequate pain management that can be mistaken for addiction.”

178.4. Purdue also distributed Exit Wounds: A Survival Guide to Pain Management for Returning Veterans and Their Families misleadingly claimed: “Long experience with opioids shows that people who are not predisposed to addiction are unlikely to become addicted to opioid pain medications.”³³⁴

179. On October 3, 2008, FDA required Purdue to develop Risk Evaluation and Mitigation Strategies (REMS) for OxyContin, finding that “FDA has determined that OxyContin is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients’ decision to use, or continue to use OxyContin.”³³⁵

180. Despite the recognized “serious risks” with OxyContin, Purdue expanded its promotion of OxyContin.³³⁶

³³⁴ SFC00005694 at 107.

³³⁵ PDD8901580306 at 2. Purdue’s REMS for OxyContin identified two primary goals: “To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of OxyContin;” and “to inform patients and healthcare professionals about the safe use of OxyContin.” Risk Evaluation & Mitigation Strategy for OxyContin, PPLPC016000016240 at 2, April 1, 2010. To accomplish these goals, Purdue stated it would provide focused education and training to healthcare providers regarding the potential risk of addiction and abuse with OxyContin. *Id.* at. 4.

³³⁶ Purdue introduced an abuse-deterrent formulation of OxyContin in 2010, and obtained labeling in 2013 that “OxyContin is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse.” https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf. This did not prevent people from abusing OxyContin orally, *see* PPLP003399733, or from seeking out other drugs to abuse, *see* Evans, William N., Ethan MJ Lieber, and Patrick Power. “How the reformulation of OxyContin ignited the heroin epidemic.” *Review of Economics and Statistics* 101.1 (2019): 1-15 (finding that “each prevented opioid death was replaced with a heroin death”). Purdue stated in 2009, “we understand that introduction of this reformulation may lead to abusers shifting to other opioids.” PDD8901592911 at 6. Furthermore, according to Purdue research from 2015, 82.7% of abusers initiated abuse by taking the drug orally, and by time of treatment admission, 54% of patients admitted to treatment abused the drug this way at least some of the time. PPLP003399733 at 34-35. Notwithstanding, Purdue’s 2014 research found that “majority [of prescribers] consider [ADF] an advantage in the treatment of chronic pain and/or say it has a favorable impact on their perception of opioids.” PPLPC019000902762 at 11.

180.1. In an October 2011 presentation, Purdue instructed its sales force to “extend average treatment duration in appropriate patients” in order to attain their sales target of \$3.9 billion for OxyContin. This instruction was identified as a “strategic imperative” for the company despite growing evidence linking duration of use and abuse of opioids.³³⁷

180.2. In addition, Purdue created a September 13, 2013 presentation that focused on “OxyContin growth opportunities.”³³⁸

180.3. In a July 11, 2014 presentation, Purdue’s Marketing department identified that its sales objective was to “[a]chieve OxyContin Tablet sales of \$1.98 billion” with a marketing program driven by its sales representatives.³³⁹

181. In my opinion, Purdue failed to take reasonable steps to correct its misleading statements and continued to expand the opioid market.

182. As discussed above, Purdue's marketing of OxyContin changed the manner in which opioids were prescribed by healthcare providers. Following Purdue, other manufacturers of opioids adopted to varying degrees marketing strategies and messages that were similar to those employed by Purdue, while also seeking to distinguish their products from Purdue’s OxyContin, and thereby contributed to the change in the practice of medicine and the opioid abuse epidemic.

183. These marketing strategies and messages included the following:

- The risk of addiction with opioids is low or rare
- That one opioid has lower abuse potential or is safer than other opioids
- Minimization of the risk of abuse associated with higher doses of opioids

³³⁷ PPLPC02000385142 at Slide 49.

³³⁸ PPLP004001344.

³³⁹ PPLP003541889 at 13, 44.

- Promotion of the unsubstantiated concept of "pseudoaddiction"
- Promotion of opioids for uses beyond their approved indications and without substantial evidence
- Overstatement of the benefit of opioids with respect to quality of life or functionality
- Misleading claims regarding the abuse-deterrent properties of opioids

VI. ENDO

A. Overview

184. Between 1997 and 2018 Endo promoted or sold various opioid products including Percocet and Opana extended release (ER) and Opana ER reformulated.³⁴⁰

185. Like Purdue and other opioid manufacturers, Endo supported efforts to expand the use of opioids by changing the way healthcare providers view and treat pain.

186. As set forth below, through its support of pain advocacy organizations and development of branded and unbranded promotion, Endo contributed to the expansion of the pain treatment market by promoting pain as an often under-treated condition requiring the use of potent opioid products. In doing so, Endo minimized the risks associated with opioids and misleadingly suggested to healthcare providers that its branded products, Percocet and Opana ER, could be used with minimal risk of abuse and addiction and for uses that had not been shown to be safe and effective by substantial evidence. In parallel with its unbranded promotion, Endo promoted Percocet, Opana ER and Opana ER reformulated in a manner that overstated their benefits and understated their risks—again, telling healthcare providers that these products could be used with minimal risk of abuse and addiction.

³⁴⁰ Other products marketed or sold by Endo include Percodan, Endocet (generic Percocet), Endodan (generic Percodan), generic MS Contin, and generic Oxycontin extended release. ENDO-OPIOID-MDL-02228542 at 10; *see also* ENDO-OPIOID_MDL-04919462.

B. Percocet

187. Percocet is an immediate release combination tablet of acetaminophen and oxycodone, which is a full opioid agonist with relative selectivity for the mu-opioid receptor.³⁴¹

188. Percocet was approved for sale in the United States in 1976.³⁴² Between 1976 and 1999, Percocet was available in 5mg strength only and was marketed by DuPont Merck.³⁴³

189. In 1997, Endo acquired a number of drugs, including Percocet, in a selective buyout of DuPont Merck.³⁴⁴

190. Percocet is Endo's second largest selling opioid to date with over \$1.7 billion revenue.³⁴⁵

1. Endo's Marketing Strategy for Percocet

191. Although DuPont's exclusivity on Percocet had expired by the time Endo purchased the drug, according to Endo's Business Plan and Marketing Strategy for Percocet, Endo planned to obtain approval for higher dosages of the drug, which would allow it to market those dosage strengths during a period of exclusivity and "[o]pportunistically capture share from OxyContin in [the] chronic market."³⁴⁶

192. As described in an April 26, 2002 Endo Quarterly Business Review, a key strategy for Percocet was "[c]onvert[ing] current 5/325mg writers to new Percocet 7.5/325 and 10/325."³⁴⁷ This strategy supported Endo's larger plan of "[e]xpanding and [a]ccelerating usage

³⁴¹ March 2017 Percocet Label.

³⁴² <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=085106>.

³⁴³ ENDO-CHI_LIT-00543478 at 5.

³⁴⁴ See <http://www.endo.com/about-us/history> (last visited Mar. 2, 2019).

³⁴⁵ *Id.*

³⁴⁶ ENDO_DATA-OPIOID_MDL-00000001-0019.

³⁴⁷ ENDO-04908522 at 171.

of Percocet 7.5/325 and 10/325 into the overall oxycodone market during period of exclusivity.”³⁴⁸

2. FDA Approval of Additional Percocet Tablet Strengths

193. On July 26, 1999, Endo obtained approval for Percocet strengths of 7.5/500mg and 10/650mg.³⁴⁹ When Endo’s exclusive right to sell these Percocet strengths expired, Endo sought approval of new Percocet tablets in the 7.5/325 and 10/325 strengths.³⁵⁰ Endo obtained approval of these new strengths on November 23, 2001.³⁵¹ These new strengths contained the same amount of oxycodone as the Percocet tablets approved two years earlier but contained less acetaminophen.³⁵²

3. Endo Funded Promotional Activities for Percocet; Those Activities Understated the Risks of the Entire Class of Opioids

(a) Endo Funded Promotional Activities to Market Percocet

194. Endo’s promotional plans for Percocet included using medical “education” to market Percocet.

194.1. In the “1998 Mid-Year Update on Goals & Objectives” for Endo’s Clinical Development and Education division, Endo’s medical “education” efforts included promotional activities: “[w]orking with sales and marketing teams to successfully execute . . . the Perco variants”³⁵³ and “accelerat[ing] the expansion of

³⁴⁸ ENDO-OPIOID_MDL-04136658 at 7.

³⁴⁹ ENDO-OPIOID_MDL-05396425 at 1. On July 2, 1999, Endo obtained approval for 5/325 mg and 2.5/325mg strengths of Percocet. ENDO-OPIOID_MDL-03453422 at 1. Endo re-launched Percocet 2.5/325 mg in February 2004. *See* ENDO-OPIOID_MDL-03265858 at 2.

³⁵⁰ *See* ENDO-OPIOID_MDL-03388210 at 18 (“[c]onvert current 7.5/500, 10/650 and 5/325 users to new strengths”).

³⁵¹ ENDO-OPIOID_MDL-03453420 at 1.

³⁵² Endo obtained FDA approval for 2.5mg Percocet tablet strengths on July 2, 1999. *See* ENDO-OPIOID_MDL-03453422 at 1.

³⁵³ Linda Kitlinski Depo. Tr. Ex. 1 (ENDO-OPIOID_MDL-05967764).

Endo's branded pain management market through focused educational and Phase IV initiatives" by "[d]evelop[ing] and leverage[ing] strategic alliances with key regional, national and international professional organizations which impact publications, practices and standards of care. (1-4Q 1998)."³⁵⁴

194.2. Similarly, and aligning with Endo's launch of Percocet in 1999, Endo's "1999 Objectives" for its Clinical Development and Education division included a focus on promoting its newly launched Percocet tablets by "[p]artner[ing] with sales and marketing to identify, prioritize and capitalize on educational opportunities which drive attainment of sales quotas," "[w]ork[ing] with sales and marketing teams to successfully launch Percocet 2.5, Percocet 5mg blue, Percocet 7.5mg, Percocet mg,"³⁵⁵ and "[d]evelop[ing] and/or expand[ing] relationships with national professional organizations related to newly-launched products (e.g. American Pain Society) (1-4Q 1999)."³⁵⁶

194.3. An Endo plan for its Clinical Development and Education division entitled "The Critical Connection for Success in 2000 and Beyond," identified objectives that focused on expanding the use of its products, such as Percocet, including: "[a]ttain/exceed financial objectives for promoted products" and "[e]xpand usage of current products by developing and leveraging strategic relationships/alliances,"³⁵⁷ "[e]xpand awareness & usage of Percos ... through acute pain initiatives,"

³⁵⁴ ENDO-OPIOID_MDL-05967764 at 5.

³⁵⁵ Linda Kitlinski Depo. Tr. Ex. 2 at 1 (ENDO-OPIOID_MDL-03258200)

³⁵⁶ ENDO-OPIOID_MDL-03258200 at 1; *see also* Linda Kitlinski Depo. Tr. 68:1-14, 69:8-73:2. Another objective identified by Endo in 1999 included "[u]tiliz[ing] strategic educational program placement and one-on-one discussions with the pain community at national/regional conferences to increase awareness of Endo's newly-launched products. (1-4Q 1999)." *Id.*

³⁵⁷ Linda Kitlinski Depo. Tr. Ex. 3 at 6 (ENDO-OPIOID_MDL-02344002 at 6).

“[s]upport/develop initiatives that combat opioiphobia” “[u]tilize new JCAHO standards as impetus to establish pain mgmt. as a priority w/PCP’s, RPh’s, Neuros.”³⁵⁸

194.4. A 2003-2007 Endo Business Plan reiterated that Endo’s vision in 2001, the same year it obtained approval to market additional Percocet tablets, was to “Drive” the Practice of Pain Management.”³⁵⁹

195. In addition, Endo developed its own pain advocacy organization, the National Initiatives on Pain Control (NIPC), that it funded to advance medical “education” materials that included misleading claims about pseudoaddiction.

195.1. In 2001, NIPC produced the newsletter, *Pain Management Today*, published by Professional Postgraduate Services for healthcare providers.³⁶⁰ This newsletter included a section titled “Key Terms For Opioid Analgesics,” which defined “Pseudoaddiction” as “behaviors that might seem aberrant, but actually indicate inadequate treatment of pain. The behaviors resolve when the pain medication is increased and appropriate analgesia is obtained.”³⁶¹

195.2. NIPC also produced a continuing medical education (CME) presentation in 2002 titled “Advances in Opioid Analgesia: Maximizing Benefit, Minimizing Harm,” claiming that “[p]seudoaddiction” is “behavior suggestive of addiction caused by

³⁵⁸ ENDO-OPIOID_MDL-02344002 at 12. This plan also identified “Unbudgeted Tactics” such as a “National visiting faculty program”³⁵⁸ described as “[c]ritical to expand base of prescribers & avg. # of scripts written” and noted “[e]ffectiveness of ‘peer-to-peer’ influence well-documented.” *Id.* at 22.

Linda Kitlinski Depo Tr. 75:22-24, 76:1-15; 96:19-97:1 (agreeing that “another strategy of [Clinical Development and Education] in the year 2000 was to use JCAHO as an impetus to establish pain management as a priority with primary care physicians.”)

³⁵⁹ ENDO-OPIOID_MDL-04908487.

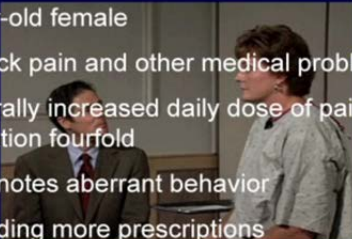
³⁶⁰ ENDO-OPIOID_MDL-01605952 at 1.

³⁶¹ ENDO-OPIOID_MDL-01605952 at 4.

undertreatment of pain,”³⁶² and providing a case history of a hypothetical patient that allegedly showed signs of pseudoaddiction:³⁶³

Case History #3: 46-year-old patient with back pain on multiple medications

- 46-year-old female
- Low back pain and other medical problems
- Unilaterally increased daily dose of pain medication fourfold
- Family notes aberrant behavior
- Demanding more prescriptions
- Is she addicted?



42

195.3. In the speaker notes for this slide, NIPC included the following points:

- As it turns out, this patient’s aberrant behaviors are evidence of pseudoaddiction.
- The concept of pseudoaddiction requires elucidation. Some patients may exhibit aberrant behaviors that suggest they have become addicted to their pain medications. The patient may become angry or defensive should any of these demands or behaviors be challenged or thwarted.
- In reality, this patient is not addicted, but is reacting to what might be termed undertreatment of her pain. It is important to realize that not all “addict-like” behavior is an infallible sign of addiction. It might also be a sign of an additional, perhaps as yet undiagnosed, pathology. In this case, the patient’s self-medication and demands for more medication are responses to the intense pain caused by metastasizing breast cancer.³⁶⁴

³⁶² KP360_OHIOMDL_000344240 at 41.

³⁶³ KP360_OHIOMDL_000344240 at 48.

³⁶⁴ KP360_OHIOMDL_000344240 at 48.

195.4. In another NIPC CME presentation, the speaker notes encouraged the aggressive use of opioids, stating that “[f]ailure to manage chronic pain aggressively may result in ongoing pain, poor functionality, and patient desocialization.”³⁶⁵

195.5. Similarly, a presentation to the Endo sales force entitled “Barriers to Effective Pain Management,” dated April 23, 2003, explained that “Patient Barriers to Pain Relief” included “Pain medication-related fears” such as “fear of addiction” and after describing addiction stated that “[b]ehaviors suggestive of addiction (e.g., drug seeking behavior) which may occur when patients are not receiving adequate pain relief. If pseudo-addiction, behavior will cease if pain is adequately treated by adjustment in opioid dose.”³⁶⁶

196. Endo also financially supported and was involved with other pain advocacy organizations that put forth “educational” materials and activities that falsely claimed that the risk of opioid addiction had been exaggerated.

196.1. For example, between 1998 and 2003, Endo provided more than \$484,000 in financial support to the American Pain Society (APS).³⁶⁷ As part of those payments to APS, Endo and APS entered into an “agreement” where Endo committed to “\$25,000 (\$10,000 in 1998; \$15,000 in 1999) to the guideline development process” and in exchange Endo’s “CD& E [Clinical Development and Education division] will sit on the

³⁶⁵ KP360_OHIOMDL_000345871 at slide 100 (p.119).

³⁶⁶ ENDO-OPIOID_MDL-02002702 at 12; *see also* ENDO-OPIOID_MDL-02829101 at 62 (slides in an Endo Opioid Analgesics Advanced Sales Training dated April 22, 2003 teach that barriers to appropriate opioid usage in the management of pain include “[m]isunderstanding of common definitions used in pain and addiction medicine” including “[p]seudoaddiction defined as “behaviors similar to addiction,” “[c]aused by undertreatment of pain,” and “[r]esolves upon institution of adequate pain treatment). *Id.* at 7-11.

³⁶⁷ ENDO-OR-CID-00632998 at 7-8. Between 1998 and 2012, Endo made total payments of at least to the APS of \$4,468,253.10.

founding members' guideline committee and provide input into topics for guideline development, as well as suggestions of clinicians for participation in the guideline development process, methods of dissemination/adoptions.”³⁶⁸

196.2. Endo also provided more than \$75,000 to the Joint Commission (formerly known as the Joint Commission on Accreditation of Healthcare Organizations or “JCAHO”) with the objective of “establish[ing] pain management as a priority with PCPs, RPhs, Neuros.”³⁶⁹

196.3. Other organizations that Endo had “develop[ed] and leverage[d] strategic alliances” with by 1998 included:

International Association for the Study of Pain (IASP), American Pain Society (APS), American Academy of Pain Management (AAPM), the American Pain Foundation (APF), the Cochrane Collaboration Group, the American Geriatric Society, and staff at the National Institute of Health/National Institute of Dental Research (NIH/NIDR).³⁷⁰

196.4. By 2004, Endo had “[w]ell-established relationships w/ national/regional societies to support and provide input on major initiatives” with following organizations:

APS, AAPMed, AAPMgmt, IASP, APF, ASPMN, ONS, MASCC, AAFP, ACP, AAN, STFM, ASAM, AOA, ASPAN, AACPI, ASHP, ACPA, NPF, RSDSA, AHS, NHF, ACHE, AAPMR, ACR, AGS, ASRA, AANA, ASA, NSSORA, AAPA, AAHPM, AANP.³⁷¹

³⁶⁸ Linda Kitlinski Depo. Tr. Ex. 4 (ENDO-OPIOID_MDL-06234663). Endo’s involvement in developing APS guidelines was reiterated in the “1998 Mid-Year Update on Goals & Objectives” for Endo’s Clinical Development and Education division, which stated “through relationships developed with the APS Board of Directors, [Endo] was successful in convincing APS to include clinical education representatives from industry to actively participate on the APS Guideline Development, Dissemination, and Implementation Committee. (APS taking over AHCPR role in pain guideline development.)” ENDO-OPIOID_MDL-05967764 at 5.

³⁶⁹ *Id.* at 12.

³⁷⁰ ENDO-OPIOID_MDL-05967764 at 5. In addition, Endo provided a grant to Professional Postgraduate Services (PPS) that PPS used “to develop and begin implementation of a continuing medical education program on acute and chronic pain conditions.” KP360-OHIOMDL_000383569. Endo was permitted to make recommendations for CME physician-speakers. *Id.*

³⁷¹ ENDO-OPIOID_MDL-01139611 at slide 32. APS (American Pain Society); AAPMed (American Academy of Pain Medicine); AAPMgmt (American Academy of Pain Management); IASP (International Association for the

197. The pain organizations supported by Endo published guidelines and other medical “education” materials that contained misleading statements regarding the safety of opioids and were used by Endo.³⁷²

197.1. For example, in 2002, APS published Guidelines for the Management of Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis, 2nd edition,³⁷³ which contained the following misleading statements: “prevalence of addiction among patients with pain who do not have a previously existing substance abuse disorder is low”³⁷⁴ and that “patients who are given doses of opioids that are inadequate to relieve their pain or whose opioid dose is discontinued abruptly or tapered too rapidly may develop characteristics that resemble addiction, which they termed iatrogenic ‘pseudoaddiction.’ Patients are often quite knowledgeable about their medications and the doses that have worked in the past. Requests for these specific medications and doses should not be

Study of Pain); APF (American Pain Foundation); ASPMN (American Society for Pain Management Nursing); ONS (Oncology Nursing Society); MASCC (Multinational Association of Supportive Care in Cancer); AAFP (American Academy of Family Physicians); ACP (American College of Physicians); AAN (American Academy of Neurology); STFM (Society of Teachers of Family Medicine); ASAM (American Society of Addiction Medicine); AOA (American Osteopathic Association); ASPAN (American Society of PeriAnesthesia Nurses); AACPI (American Alliance of Cancer Pain Initiatives); ASHP (American Society of Hospital Pharmacists); ACPA (American Chronic Pain Association); NPF (National Pain Foundation); RSDSA (Reflex Sympathetic Dystrophy Syndrome Association); AHS (American Headache Society); NHF (National Headache Foundation);, ACHE (American College of Healthcare Executives); AAPMR (American Academy of Physical Medicine & Rehabilitation); ACR (American College Of Rheumatology); AGS (American Geriatrics Society); ASRA (American Society of Regional Anesthesia); AANA (American Association of Nurse Anesthetists); ASA (American Society of Anesthesiologists); NSSORA, AAPA (American Academy of Physician Assistants); AAHPM (American Academy of Hospice and Palliative Medicine); AANP (American Academy of Nurse Practitioners).

³⁷² Further detail regarding Endo’s involvement in these pain advocacy organizations is provided below in Section XI.

³⁷³ See PKY181215547; Endo along with Abbott Immunology, Faulding Laboratories, GlaxoSmithKline, Hoechst Foundation, Janssen Pharmaceutica, McNeil Consumer Healthcare, Merck and Co., Inc., Pain Therapeutics, Inc., Pharmacia Corp./Pfizer Inc., Purdue Pharma, and Roxane Laboratories, Inc. contributed to “a common APS Guidelines Program Fund that is used for the support of all APS evidence-based clinical practice guidelines.” *Id.* at 14.

³⁷⁴ *Id.* at 95.

interpreted as necessarily indicating drug-seeking behavior.”³⁷⁵ “As a founding member of the APS guideline committee,” Endo was “entitled to access/distribute copies of the guidelines through [Clinical Development & Education division], and if approved by Endo’s PMRB, through our sales representatives.”³⁷⁶

198. In my opinion, Endo’s marketing activities misleadingly understated the risks of the entire class of opioids.

(b) Endo’s Brand Marketing of Percocet Minimized the Risks of Respiratory Depression and Abuse Associated With Higher Doses of Opioids

199. As discussed in the Purdue section, the greater the dose of opioids, the greater the risk of respiratory depression and abuse.

200. Endo’s marketing strategy for Percocet focused on encouraging the prescription of higher doses and for longer use but did not highlight the increased risks of respiratory depression and abuse.

200.1. For example, a draft 2002 Percocet Business Plan and Marketing Strategy identified key messages for Percocet as including “*Push dose higher. Use longer,*”³⁷⁷ “Continue Percocet use longer in chronic pain patients because lower acetaminophen levels,” and “Increases Percocet daily oxycodone dosage from 60mg to 120mg.”³⁷⁸

200.2. Endo’s 2002 Percocet Business Plan and Marketing Strategy also included the message “Reduction in acetaminophen means less worry about acetaminophen levels

³⁷⁵ *Id.*

³⁷⁶ ENDO-OPIOID_MDL-06234663.

³⁷⁷ ENDO-OPIOID_MDL-03388209 at 7. (Emphasis added)

³⁷⁸ *Id.* at 7; *see also* ENDO-OPIOID_MDL-04908071 at 3 (“Our goal is to convert physicians who prescribe high-strength pain alleviating drugs to the newly launched Percocet 7.5/325 and Percocet 10/325).

and greater dosing flexibility for physicians,” and “Confidence in longer term use means that physicians can reduce the need to switch to other medications.”³⁷⁹

200.3. Similarly, Endo’s 2002 Percocet sales representative detail aid touted the benefits of the increased Percocet strengths: “New Percocet 7.5/325 and 10/325 mg strengths: Effective pain management with less acetaminophen.”³⁸⁰ The detail aid also contains a chart showing the reduced acetaminophen levels in the new Percocet strengths and stated “Confidence in longer-term use with reduced acetaminophen as compared to 7.5/500 and 10/650 mg.”³⁸¹

201. Endo incentivized its sales representatives to promote higher doses to healthcare providers.³⁸²

201.1. For example, a 2002 Endo “Tsunami Launch IC Plan” incentivized the Endo sales force to meet the goal of “pushing higher doses” with “rewards that increased steeply” for “deeper penetration into the *high-strength* [Oxy/APAP] market”—defined as Percocet 7.5/325 and 10/325 and all Oxy/APAP 7.5/500 and 10/650 variants (Percocet, Endocet, and Generic Oxycodone/APAP).³⁸³

201.2. In addition, a presentation to Endo’s sales force titled “Endo State of the Union,” described a “Grand Prix Contest,” measured by “One Metric”—“Percocet TRx increase,” where participating sales representatives and district managers could compete

³⁷⁹ *Id.*

³⁸⁰ ENDO-OPIOID_MDL-04929187 at 3.

³⁸¹ *Id.*

³⁸² See <http://www.endo.com/about-us/history> (last visited Mar. 2, 2019).

³⁸³ (Emphasis added). ENDO-OPIOID_MDL-04908071 at 4. The “high strength Oxy/APAP market segment” was defined to include Percocet 7.5/325 and 10/325, all Oxy/APAP 7.5/500 and 10/650 variants (Percocet, Endocet, and Generic Oxycodone/APAP).

for prizes and the “the opportunity to drive one of six BMWs as their company car starting in mid 2004.”³⁸⁴

202. According to Endo, its promotional efforts resulted in an increase in sales of higher doses of Percocet.

202.1. By 2001, Endo documents characterized the strategy to launch more Percocet tablet strengths “as a success.”³⁸⁵

202.2. According to a Percocet Awareness & Message Tracking Study described in Endo’s 2002 Percocet 1st Quarter Business Review, “the sales message” [in the Percocet 7.5/325 & 10/325 detail aid] worked. “Approximately 90% indicated that [they] have prescribed the new strengths recently”³⁸⁶ and “[m]ore than 60% indicate their prescribing will increase in the future.”³⁸⁷

203. In my opinion, in promoting higher doses of Percocet, Endo misleadingly minimized the risks of respiratory depression and abuse associated with higher doses of opioids.

(c) Endo Overstated the Benefits of Percocet With Respect to Quality of Life

204. Similar to Purdue’s marketing of OxyContin, Endo’s sales training instructed its sales force to make statements based on a single open label study that Percocet improved the quality of life of patients.³⁸⁸ A single open label study does not constitute substantial evidence in which to draw promotional claims.³⁸⁹

³⁸⁴ ENDO-OPIOID_MDL-04911467 at 49; *see also* ENDO-OPIOID_MDL-05589327 at 2.

³⁸⁵ ENDO-OPIOID_MDL-02740383 at 7.

³⁸⁶ ENDO-OPIOID_MDL-049271976 at 16.

³⁸⁷ *Id.*

³⁸⁸ ENDO-OPIOID_MDL-04908364 at 13-14 (“Patients received a statistically significant improvement in all seven QOL parameters and received 39% improvement in overall QOL,” and “Improvement in QOL for patients.”); *see*

205. Statements regarding an improved quality of life associated with Percocet were likewise made to healthcare providers. For example, in a detail aid, Endo stated “New Percocet significantly reduced pain interference with improvement in overall mood, general activity, walking, work, relations, sleep, and enjoyment” and also cited to the open-label clinical trial in support of this claim.³⁹⁰

206. In my opinion, Endo overstated the benefits of Percocet with respect to quality of life.

4. As Reports of Percocet Abuse Grew, Endo’s Promotion and Sales of Percocet Increased

207. After receiving FDA approval to market additional strengths of Percocet in 1999, Endo’s promotional budget of Percocet grew to \$4,256,000 by 2003³⁹¹ with Endo describing itself as the “[c]ompany that Percocet built” and the “company that built Percocet.”³⁹² Sales of Percocet increased from \$40 million to \$214 during this timeframe³⁹³ with a total of 942,959,500 Percocet tablets added to the market by Endo.³⁹⁴

208. Also during this timeframe, evidence of Percocet abuse was rising.

also id. at 15 (“Low Back Study Data . . . Representatives will start using the revised master sales aid after all the district meetings conclude. Week of 4/15.”).

³⁸⁹ In promotion, treatment claims must generally be supported by “substantial evidence” or “two, adequate and well-controlled trials.” An open-label clinical trial is insufficient to satisfy this requirement.

³⁹⁰ ENDO-OPIOID_MDL-04929187 at 7-8, 3.

³⁹¹ ENDO-OPIOID_MDL-04136658 at 11.

³⁹² ENDO-OPIOID_MDL-01139611 at 11.

³⁹³ ENDO-OPIOID_MDL-01139611 at 12.

³⁹⁴ ENDO_DATA-OPIOID_MDL-00000025-41.

208.1. According to an Endo document entitled “Percocet History” “[f]rom 2000-2002, Oxycodone and Hydrocodone accounted for approximately 70% of all narcotic analgesic drug abuse” with Percocet among the top three opioids abused.³⁹⁵

208.2. The same document identified street names for Percocet such as “Percs” and “Percies” and street names for oxycodone products as “Hillbilly Heroine” and “Killer.”³⁹⁶

208.3. According to the National Survey on Drug Use and Health (NSDUH) Report, by 2002 “[a]pproximately 9.7 million individuals age > 12 had used Percocet, Percodan or Tylox for non-medical use at least once.”³⁹⁷

209. In my opinion, as reports of Percocet abuse grew, Endo’s promotion and sales of Percocet increased.

C. Opana ER

210. Opana ER is oxymorphone in an extended release tablet.³⁹⁸ Oxymorphone is an opioid agonist that is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses.³⁹⁹

³⁹⁵ ENDO-CHI_LIT-00543478 at 7. “From 2000-2002, Oxycodone and Hydrocodone accounted for approximately 70% of all narcotic analgesic drug abuse.” *Id.*

³⁹⁶ *Id.* at 9.

³⁹⁷ ENDO-CHI_LIT-00543478 at 7.

³⁹⁸ Opana ER original label (2011). Opana ER is still sold in generic form. In 2010, Endo and Impax Laboratories, Inc. entered into an agreement whereby Impax was authorized to commence selling a generic version of the original formulation of Opana ER on January 1, 2013. Under the terms of this agreement, Impax would pay Endo 28.5% of the sales of its product provided Endo’s sales during the preceding period hit certain benchmarks. EPI001695037 at 12.

³⁹⁹ *Id.*

211. Endo received initial FDA approval to market Opana ER on June 22, 2006 and it has since been withdrawn from the market.⁴⁰⁰ In 2011, Endo received approval to market Opana ER reformulated,⁴⁰¹ which is discussed in the section below.

212. In approving Opana ER, the FDA's Clinical Review stated "[a]s an opioid agonist oxymorphone has similar pharmacological effects as the other drugs of the same class as described in the product labeling for opioid drugs. The major safety issues with the use of opioids are their potential for . . . drug abuse and addiction."⁴⁰²

213. Opana ER and Opana ER reformulated have generated over \$2 billion in combined revenue for Endo.⁴⁰³

⁴⁰⁰ Endo received approval for Opana ER 5, 10, 20 and 40 mg on June 22, 2006 for "the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period time." ENDO-OPIOID_MDL-00298948 at 1. On February 29, 2008, FDA approved 7.5mg, 15mg, and 30mg strengths of Opana ER tablets. These dosages were approved for the same indication.

Opana ER was approved based on enriched enrollment studies. Enriched enrollment is one of several enrichment strategies for clinical trials that can be used according to FDA Guidance to demonstrate efficacy of a drug. *See* FDA Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products (Dec. 2012)

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf> (accessed Mar. 11, 2019) ("Clinical trials are not designed to demonstrate the effectiveness of a treatment in a random sample of the general population," rather "sponsors use a variety of strategies to select a subset of the general population in which the effect of a drug . . . can more readily be demonstrated."). Enriched enrollment design determines the study population by screening out patients who are non-responsive or suffer serious side effects. *See generally*, FDA Draft Guidance for Industry: Analgesic Indications: Developing Drug and Biological Products at 16 (Feb. 2014),

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf> (accessed Mar. 11, 2019) ("2014 Guidance"). First in an open-label titration period, subjects are administered the test drug and titrated to an individually tolerable and effective dose. *Id.* "Only those subjects who can be successfully titrated using prespecified criteria . . . with no intolerable adverse events" proceed and are "randomized to remain on investigational drug or to placebo." *Id.*

The FDA has approved of use of enriched enrollment in clinical trials of opioids. *See e.g., id.* (explaining that it "can be useful for decreasing early dropouts caused by adverse events."). However, enriched enrollment has been criticized. *See generally* ENDO-OPIOID_MDL-04239494 at 2-7.

⁴⁰¹ The approved label for Opana ER reformulated did not include an abuse deterrent labeling claim or a description of the physiochemical properties of the drug. *See* EPI001314350.

⁴⁰² ENO000028976 at 57.

⁴⁰³ ENDO-DATA-OPIOID_MDL-00000008-00000019.

1. Endo's Marketing Strategy for Opana ER

214. According to a 2002 Opana ER Marketing Plan, Endo's "strategic intent" in developing Opana ER was to displace OxyContin and MS CONTIN "as the brand of choice for moderate-severe chronic pain requiring strong opioid analgesia for an extended period of time."⁴⁰⁴

215. During the development of Opana ER, widespread reports of OxyContin abuse and diversion prompted negative attention and investigations by federal and state agencies,⁴⁰⁵ which Endo identified as a point in which to differentiate Opana ER as "[p]hysicians are looking for an alternative to OxyContin because of the media attention and stigma."⁴⁰⁶

215.1. In a 2002 Opana ER Risk Management presentation, Endo noted that it planned to "[c]reate market environment prior to launch that ensures rapid uptake and adoption of [Opana ER]" by "remov[ing] barriers—real and perceived—to prescribers."⁴⁰⁷

215.2. Similarly, in 2002 Opana ER Marketing Plan, Endo stated it would "proactively neutralize opioid abuse issues."⁴⁰⁸

⁴⁰⁴ END00001522 at 11; *see also* ENDO-OPIOID_MDL-04095507 at 21 ("[p]osition Opana as a competitor for oxycodone ER and ER morphine's."). Prior to the approval of Opana ER, the extended release market was dominated by Purdue's OxyContin, which had \$752 million in sales in 2006. *See* PPLPC022001014861.

⁴⁰⁵ *See, e.g.*, ENDO-OPIOID_MDL-04095507 at 5 ("Endo Risk Management Strategy Global Issues": Receptiveness of market to potent, chronic-use opioids has been dampened because of abuse and diversion issues with Purdue's OxyContin, played prominently in the media"); ENDO-OPIOID_MDL-03006242 (OxyContin Abuse and Diversion and Efforts to Address the Problem, General Accounting Office Report, Dec. 2003).

⁴⁰⁶ ENDO-OPIOID_MDL-04095507 at 10; *see also* ENDO-OPIOID_MDL-04095507 at 6 ("Pain Specialists/Policy Makers" "Clearly afraid of abuse and diversion."); END00001522 at 13 ("Concerns over abuse in the spotlight" with "doctors more hesitant to write extended release opioids"); *see also* ENDO-OPIOID_MDL-02002513 at 63; END00000923 at 9; ENDO-CHI_LIT-00550851 at 16; ENDO-CHI_LIT-00552969 at 19.

⁴⁰⁷ *Id.* at 13.

⁴⁰⁸ *Id.* at 14.

216. In addition, to overcome the negative association with opioids, Endo strategized that unbranded marketing, i.e. marketing not directly tied to Opana ER but to opioids in general, would be necessary to rebuild physician comfort with prescribing opioids—and ultimately physician comfort with prescribing Opana ER and would also provide a return on investment for Endo.

216.1. A slide in a March 25, 2002 Opana ER Risk Management Presentation entitled “ROI for [Opana ER] stated: “Potential sales of [Opana ER] depend directly on prescribers’ comfort level with risk of abuse and diversion.”⁴⁰⁹

216.2. In a June 10, 2003 email from Endo’s Senior Director of Clinical Development and Education, Linda Kitlinski, stated that a successful launch of Opana ER needed a CME program by the National Initiative on Pain Control (NIPC), an organization solely supported and funded by Endo,⁴¹⁰ as CMEs are the “only way to credibly talk about opioids in this day and time.” Ms. Kitlinski added that she couldn’t “see how we can successfully launch [Opana ER] without [CME]” concerning opioids.⁴¹¹

216.3. A June 9, 2003 email from Linda Kitlinski to various employees regarding “NIPC Input Needed for Meeting” stated: “Guyz . . . Please hit reply all and let us know 1) your opinion on what the focus . . . of the new module should be. Items to consider in marking this recommendation: a) what will provide the best educational ROI for Endo; b) what the Faculty/Education Council will likely be most receptive to; and c) what will generate best interest/turnout. Given the level of interest and issues surrounding opioids,

⁴⁰⁹ ENDO-OPIOID_MDL-04095507 at 19.

⁴¹⁰ END00152457 at 10.

⁴¹¹ ENDO-OPIOID_MDL-02261843 at 1; *see also* Opana ER 2007-2011 Business Plan, ENDO-CHI_LIT-00545916 at 5 (“Regulatory/Legislative- “More restricted marketing.”)

coupled with our anticipated launch of [Opana ER/IR], I think opioids should be the focus.”⁴¹²

216.4. In this same email, Ms. Kitlinski’s colleague at Endo, Nancy Alvarez, stated: “Opioids should be the focus . . . Nothing new to add except that there is a great need for education as voiced by the last group of advisors . . . They also voiced great concern over the need for pharmacists to receive information as they view them as a major barrier jockeying for position with managed care . . . The return on investment may be to have product available when prescriptions are written.”⁴¹³

216.5. A November 13, 2003 email from Vin Tormo, Clinical Liaison in Clinical Development & Education at Endo regarding “NIPC OPIOID Cinci Program-Fantastic Feedback” stated: “Glad that your recommendation to have the opioid program in Cincinnati paved the way towards, and lessened the fear of appropriately prescribing opioids.”⁴¹⁴

216.6. In the same email Ms. Kitlinski responded on November 16, 2003 and stated: “CONGRATULATIONS on working together to really optimize the value of the NIPC programs for the physicians in your area . . . As we saw with the return on education study conducted this year, the effectiveness of well-planned CME content and well-executed audience recruitment is truly a ‘winning combination.’”⁴¹⁵

216.7. An NIPC invitation invited healthcare providers to “[j]oin your colleagues for an interactive case-based DISCUSSION on **Advances in Opioid Analgesia:**

⁴¹² *Id.* at 2.

⁴¹³ *Id.* at 2.

⁴¹⁴ ENDO-OPIOID_MDL-01928285 at 1.

⁴¹⁵ *Id.*

Maximizing Benefit While Minimizing Risk Dinner Dialogue Series on November 8, 2006” with Grace Forde, MD and Charles Argoff, MD in Roslyn, NY.⁴¹⁶

216.8. In an undated audio recording of an NIPC Dinner Dialogue program entitled “Advances in Opioid Analgesia, Maximizing Benefit While Minimizing Risk,” Dr. Grace Ford told participants “Initial patient assessment. Why assess pain? Well, inadequate assessment is a major, major barrier to treatment. Appropriate decision regarding opioid therapy require[s] a comprehensive assessment. And comprehensive assessment is required by JCAHO. And pain is the Fifth Vital sign. You have to treat patients’ pain adequately. If not you can and you will be sued . . . So we have to be proactive in treating patients’ pain. Assessment is required by opioid treatment guidelines.”⁴¹⁷

217. In addition to rebuilding the opioid brand, Endo formed an Issues Management team prior to the launch of Opana ER to address concerns that “[m]issue/[a]buse risk perception may create negative environment and a PR crisis OxyM and Endo pain franchise”⁴¹⁸

217.1. In a April 27, 2006 email Issues Management Team members forecasted potential harm with Opana ER including: “[d]eath of teen abuser,” “crime reports (pharmacy break-ins, etc) attributed to OxyM seeking,” “Dateline NBC or 60 Minutes type investigation into the approval of another abusable opioid,” “Endo’s Percocet abuse

⁴¹⁶ KP360_OHIOMDL-000003328.

⁴¹⁷ KP360_OHIOMDL_000095691 (17:40-18:15). When asked at her deposition whether Endo paid for a program that threatens to sue doctors for not treating pain adequately, Ms. Kitlinski testified that “Endo cannot control . . . the faculty’s opinions or comments,” but admitted she could not recall ever filing a complaint against Dr. Ford and agreed that Endo continued to support the NIPC until 2012 or 2013. Linda Kitlinski Depo. 219:9-12, 219:16-5, 221:8-9, 12-13, 15-18, 21-24. Ms. Kitlinski also testified that as of 2014, “[t]here were no studies of longer duration than one year” of long-term opioid therapy in patients with chronic pain versus no opioid therapy or nonopioid alternative therapies that evaluated outcomes at one year or longer.” *Id.* at 232:9-15, 18-24.

⁴¹⁸ ENDO-CHI_LIT-00543506 at 3.

history is the subject of investigational reports citing Endo's lack of responsible approach in the past," and "Doctor charged with Rx Fraud in writing [Opana ER]" among other potential crises.⁴¹⁹

217.2. Likewise in early 2006, Endo hired public relations and crisis management company, Waggener Edstrom.⁴²⁰ Waggener Edstrom identified Opana ER weaknesses including (1) product abuse liability is similar to morphine; (2) crushing product or combining it with alcohol can trigger fatal overdose;⁴²¹ and the potential for a "[c]lass-action lawsuit against Endo regarding Opana marketing" and "[r]are, serious adverse event occurs."⁴²²

217.3. In response to these concerns, Endo developed a strategy that included enlisting "Assistance of Key Advocacy Groups," "Prepar[ing] for Positive/Negative Scenarios," Engaging Key Law Enforcement, Federal DEA, U.S. Attorney, State AG's, focusing on OxyContin 'Hot States', and Rapid Response to Critics/Issues,⁴²³ and engaging state regulatory associations and continuing rapid response to media, public constituencies.⁴²⁴

⁴¹⁹ ENDO-OPIOID_MDL-00849563 at 2.

⁴²⁰ ENDO-CHI_LIT-00543384.

⁴²¹ *Id.* at 17.

⁴²² *Id.* at 20.

⁴²³ END00004340 at 3.

⁴²⁴ *Id.* at 3.

2. Endo Promoted Opana ER in a Manner that Understated Its Risks and Overstated Its Benefits.⁴²⁵

(a) Endo Falsely Marketed Opana ER as Having a Lower Abuse Potential and as Safer than Other Opioid Products

218. Oxymorphone, the opioid molecule in Opana ER, has a history of abuse that can be traced back to the 1960s when it was sold by Endo in immediate release form under the trade name Numorphan.⁴²⁶

218.1. In a May 2011 Drug Intelligence Brief, the DEA's Philadelphia Division Intelligence Program described Numporphan as a popular opioid of abuse.

In the early 1970s, oxymorphone in the form of Numorphan instant-release tablets was one of the most sought-after and well-regarded opioids of the class IV drug using community. Popularly known as 'blues' for their blue coloring, the tablets contained very few insoluble ingredients—making them extremely easy to inject—and they were dangerously potent when used intravenously. 'Blues' were also considered to be especially euphoric; better than heroine or morphine."⁴²⁷

218.2. Similarly, the National Institute on Drug Abuse ("NIDA") reported in 1974 that "Numorphan (oxymorphone immediate release) . . . was found to be the object of increased abuse since its appearance in 1966." NIDA cited Numorphan's "rapid onset of action and prolonged duration of effect" as reasons for its popularity.⁴²⁸

219. Endo has likewise acknowledged that Opana ER has an abuse liability similar to other opioids.

⁴²⁵ Kristin Vitanza, Endo's Brand Manager for Opana ER, testified on behalf of Endo that all "Endo reviewed and approved [] promotional materials for . . . Opana ER, both original and reformulated . . ." "were . . . made available for use nationwide in the promotion of Opana ER." Kristin Vitanza Depo Tr. 282:11-283:3.

⁴²⁶ Numorphan was approved for sale in the U.S. in 1959. ENDO-OPIOID-MDL-00156028 at 3.

⁴²⁷ ENDO-OR-CID-00694804 at 2; *see also* WATKINS, TORRINGTON D. & CARL D. CHAMBER, DRUG ABUSE: CURRENT CONCEPTS AND RESEARCH, 307-09 (KEUP, WOLFRAM, ED., 1972) (As of 1972 "abuse of Numorphan appear[ed] to be rather widespread geographically" with "Numorphan . . . identified by its various subcultural names—numorphine, blue morphine, blue morphan, or blues . . .").

⁴²⁸ Endo's predecessor, Endo Laboratories, withdrew Numorphan immediate-release tablets from the market in 1979. ENDO-OPIOID-MDL-00156028 at 3.

219.1. The label for Opana ER warned of Opana ER's abuse liability in a prominent, Blackbox warning reserved for serious or life-threatening risks, noting an abuse liability similar to other opioids:

WARNING: Opana ER contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, *with an abuse liability similar to other opioid analgesics*. Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of . . . abuse . . .⁴²⁹

219.2. In addition, Endo's Abuse Liability Assessment for Oxymorphone Extended Release Tablets described the "Risks" of the drug as including that "Oxymorphone is an opioid agonist and a Schedule II controlled substance. It is expected to have an abuse liability similar to other strong opioid analgesics, such as morphine and oxycodone."⁴³⁰

219.3. Endo also included abuse of Opana ER as one of the risks addressed in the Risk Minimization Action Plan ("RiskMAP") for Opana ER,⁴³¹ stating "[t]he goals and objectives for this RiskMAP are to minimize the following liabilities with opioid class of drugs as it pertains to Opana ER . . . Aberrant behavior such as . . . drug abuse . . . [a]mong patients" and "[i]n the community, particularly among your adults." Robert

⁴²⁹ 2006 Opana ER Label (Emphasis in original and added). The current label for Opana ER contains a Blackbox warning with similar language regarding the abuse liability of the drug. *See* 2016 Opana ER Label (ENDO-OPIOID_MDL-00046776 at 4) ("Opana ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death.")

⁴³⁰ ENDO-OPIOID_MDL-00235234 at 36. Abuse of oxymorphone can be traced back to the 1970s. In 1974, the National Institute on Drug Abuse stated in "Drugs and Addict Lifestyles," that "Numorphan (oxymorphone immediate release) . . . was found to be the object of increased abuse since its appearance in 1966. Reasons for its popularity seem to be that it provides rapid onset of action and prolonged duration of effect." FERGUSON, PATRICIA ED., DRUGS AND ADDICT LIFESTYLES, NATIONAL INSTITUTE ON DRUG ABUSE RESEARCH, 237 (1974). In 1979, Endo withdrew Numorphan immediate-release tablets from the market. EPI000130489 at 8.

⁴³¹ EPI000750019 at 8.

Barto Dep. Tr. 1/30/2019 140:7-13, 21-141:7, 142:20-143:2 (“Endo worked with FDA to establish these goals and objectives, and these were the agreed-to goals and objectives with FDA as part of this RiskMAP.”)

219.4. Recently, on January 10, 2019, Endo’s former vice president of sales, Larry Romaine, likewise testified that Opana ER does not have “low abuse potential.”⁴³²

220. Endo witnesses testified that Endo was not permitted to market Opana ER as having less abuse.

220.1. Endo’s former Chief Compliance Officer, Colleen Craven, testified during her deposition, “I agree that Endo was not allowed to say that there was less abuse,” or “less possible diversions of Opana ER for any reason.”⁴³³

220.2. Similarly and in response to the question “you agree that Endo was not allowed to make any of these statements in this sentence about Opana ER: Less abuse, less possible diversion; cannot be crushed; none of the statements were allowed to be made, right?” Ms. Craven testified: “Correct.”⁴³⁴

220.3. Endo’s Vice President of Sales and Regional Business Director, Ronald Jackson similarly testified that it would be “improper” for Endo sales reps “to try to downplay stated risks with respect to a product.”⁴³⁵

221. Despite testimony from Endo’s witnesses that it was not permitted to market Opana ER as having less abuse liability, Endo’s sales force falsely marketed Opana ER as safer than other opioids because of reduced abuse liability.

⁴³² See, e.g., Larry Romaine Depo. Tr. 352:12-14, 16-24.

⁴³³ Colleen Craven Dep. Tr. (356:13-357:3, 357:5-7).

⁴³⁴ Craven Dep. Tr. (358:1-6).

⁴³⁵ Ronald Jackson Depo. Tr. 289:9-12.

221.1. Following the launch of Opana ER in June 2006, Endo commissioned market research to identify physician perceptions of Opana ER called Awareness, Trial and Usage (“ATU”) studies.⁴³⁶ These studies confirmed that Endo’s messages that Opana ER had low abuse potential and was safer were being delivered to physicians.

221.2. A June 2007 ATU study of physician recall/perceptions reported that “low abuse potential and safety and tolerability were regarded as the main advantage of Opana ER.”⁴³⁷

221.3. A 2008 ATU study confirmed that one year later physician perceptions remained similar. The study stated that physician awareness of Opana’s “lack of street value” led to “a perception of lower potential for street abuse.”⁴³⁸ The study also reported that physicians who anticipated prescribing increases for Opana ER over the next 6 months” cited “low abuse potential” as one of two major reasons for choosing Opana ER.⁴³⁹

221.4. Market research from 2008 indicated that “PCPs prefer hearing that the agent they select for treatment would be less risky and therefore, easier for them; they reported a sense of calm after reading the ‘simple’ statement.”⁴⁴⁰

221.5. In an Opana ER W2 IVR Vocal Response Listing examining Endo sales representative in-person sales presentations, certain doctors reported that the “main message of the most recent presentation [they] received” for Opana ER included “Less

⁴³⁶ *Id.* at 342:18-343:4.

⁴³⁷ *Id.* at 343:8-12, 343:16-344:2, 5-6.

⁴³⁸ ENDO-CHI_LIT-00547543 at 12.

⁴³⁹ *Id.*

⁴⁴⁰ ENDO-CHI_LIT-00023299 at 38.

euphoria and maybe less addictive potential,” “safe, long acting, *less abuse potential*,” and “The delivery system and *low abuse potential*.”⁴⁴¹

221.6. A December 2008 ATU Final Report stated that Opana ER had “an opportunity to build on one of its most important strengths—low abuse potential.”⁴⁴²

221.7. Endo’s market research from 2008 showed that “Low abuse Potential” was the primary factor influencing physicians’ anticipated increase in use of Opana ER.”⁴⁴³

221.8. Endo sales reps facilitated letters written by doctors to the West Virginia Medicaid Pharmaceutical & Therapeutics Committee, that understated the risk of abuse, stating “Opana ER has a unique delivery system which involves a Matrix, thus allowing it to be given twice a day. The Matrix also allows for the chance of less abuse and possible diversion since it cannot be crushed allowing for injection or nasal administration.”⁴⁴⁴

221.9. In 2009 and 2010, between 15- 21% of physicians surveyed maintained the perception that “advantages of Opana ER” included “low abuse potential.”⁴⁴⁵

221.10. Endo’s Vice President of Sales, Larry Romaine, testified that “Endo could have sent out a Dear Doctor letter to the prescribers it was servicing,” in order to correct the misperception that Opana ER had a low abuse potential and that this

⁴⁴¹ ENDO-CHI_LIT-00150080 (Emphasis added).

⁴⁴² ENDO-CHI_LIT-00547543 at 17.

⁴⁴³ ENDO-CHI_LIT-00023299 at 59.

⁴⁴⁴ ENDO-OPIOID_MDL-0380727 at 3.

⁴⁴⁵ ENDO-CHI_LIT-00023394 at 55; ENDO-CHI_LIT-00012061 at 37. Six percent of physicians interviewed reported that “[l]ow abuse potential” was the “first thing that comes to mind when [they] think of Opana ER.” *Id.* at 36.

misperception was driving their prescription decisions.⁴⁴⁶ Mr. Romaine could not recall whether such a letter was sent.

222. In my opinion, Endo falsely marketed Opana ER as having a lower abuse potential and as safer than other opioid products.

(b) Endo Minimized the Risk of Addiction Associated with Opana ER and Funded Various Pain Organizations to Likewise Minimize the Risk of Addiction

223. Oxymorphone is known to be addictive, which Endo recognized in seeking approval of Opana ER.

223.1. An article from the New England of Journal of Medicine included in the Opana ER NDA explained: “[t]here can be no doubt, however, that prolonged administration of Numorphan [oxymorphone] represents considerable addiction liability.”⁴⁴⁷

223.2. Addiction risk as it pertains to Opana ER was also one of the risks that Endo told FDA it was addressing through its Risk Minimization Action Plan (“Risk Map”) for Opana ER.⁴⁴⁸

224. Nonetheless, Endo minimized the addiction potential of oxymorphone discussed above by telling healthcare providers and patients that the risk of addiction with Opana ER and opioids was low.

⁴⁴⁶ Larry Romaine Dep. Tr. 360:9-12, 16-21, 360:24-361:14.

⁴⁴⁷ ENDO-OPIOID-MDL-00235351 at 4.

⁴⁴⁸ EPI000750019 at 8 (“The goals and objectives for this RiskMAP are to minimize the following liabilities with opioid class of drugs as it pertains to Opana ER . . . Aberrant behavior such as . . . addiction . . . [a]mong patients” and “[i]n the community, particularly among your adults.”); Robert Barto Dep. Tr. 1/30/2019 140:7-13, 21-141:7, 142:20-143:2 (“Endo worked with FDA to establish these goals and objectives, and these were the agreed-to goals and objectives with FDA as part of this RiskMAP.”)

224.1. A 2009 Opana ER “Instant Savings” card and Resource Kit promising patients up to \$300 in savings asked “What is the risk of becoming addicted to a long-acting opioid?” In response, the accompanying information kit stated “[m]ost healthcare providers who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.”⁴⁴⁹

224.2. Endo’s website for Opana, [www. Opana.com](http://www.Opana.com) broadcasted the statement “Most doctors who treat patients with pain agree that patients treated with prolonged opioids medicines usually do not become addicted” until at least 2012.⁴⁵⁰

225. Endo also delivered the misleading message that opioids have low addiction potential through pain advocacy organizations and medical societies it funded.⁴⁵¹

225.1. A December 2007 NIPC *Pain Management Today* newsletter told healthcare providers: “[p]atients are also concerned with being looked upon as ‘druggies’ even though risk of addiction in the general population treated with chronic opioid therapy is extremely low. This adds to the psychological issues that often accompany chronic pain conditions.”⁴⁵²

⁴⁴⁹ ENDO-CHI_LIT-00541205 at 7. A 2010 Oxymorphone Franchise Tactical Plan by Chad Simon, Sr. Product Manager, for the OPANA Brand, reported that the Opana Instant Savings Program had a 14% redemption rate in 2009 for a total of 58,227 redemptions in the range of \$21-25 nationally and between 4,000 and 7,000 redemptions in Ohio. ENDO-CHI_LIT-00039111 at 31.

⁴⁵⁰ END00474717 at 23.

⁴⁵¹ According to Endo’s May 2012 response to the Hon. Max Baucus and Hon. Charles E. Greeley, then Chairman and a member of the Senate Finance Committee, between 1997 and 2012, Endo paid millions of dollars to the American Pain Foundation, American Academy of Pain Medicine, American Pain Society, American Geriatrics Society, University of Wisconsin, Beth Israel Medical Center, the Joint Commission on Accreditation, and the Federal State Medical Boards. ENDO-OR-CID-00754369 at 24-32.

⁴⁵² KP360_OHIOMDL_000027041; Ms. Kitlinski testified that it was Endo’s “intent” “that doctors of all backgrounds, of all specialties, in training or in practice for a long time, had exposure to the company’s supported education programs,” including through the NIPC.” Linda Kitlinski Dep. Tr. (1/15/2019) 395:11-19, 395: 22-24, 396:1-7.

225.2. Endo also provided financial assistance to the American Academy of Pain Medicine (“AAPM”) and the American Pain Society (“APS”), and distributed to healthcare providers the 1997 AAPM/APS consensus statement, which downplayed the risk of addiction, stating that “studies indicate that the de novo development of addiction when opioids are used for the relief of pain is low.”⁴⁵³ The Consensus Statement failed to identify any of the “studies” that it claimed “indicate[d] that the de novo development of addiction when opioids are used for the relief of pain is low.”⁴⁵⁴

226. In my opinion, Endo minimized the risk of addiction associated with Opana ER and funded various pain organizations to likewise minimize the risk of addiction.

(c) Endo Falsely Told Healthcare Providers that Patients Exhibiting Signs of Addiction Could be Exhibiting “Pseudoaddiction” and in Need of Additional Opioids to Treat Pain

227. As described in the Purdue section, the concept of pseudoaddiction is not supported by substantial evidence.

228. Despite a lack of substantial evidence for the concept of pseudoaddiction, Endo included the term in its sales training materials for Opana ER.

228.1. A 2006 Endo sales training document entitled “Module 3: Oxymorphone Risk Management Program” contained a list of definitions “of five important but commonly misunderstood terms” including “Pseudoaddiction,” which it defined as a “term used to describe iatrogenic phenomenon in which a patient with undertreated pain

⁴⁵³ ENDO-OPIOID_MDL-00925807. Endo distributed the Consensus Statement including as part of its risk minimization plan for generic oxycontin and Opana ER. EPI000799695 at 14; ENDO-OPIOID_MDL-01500831 at 14.

⁴⁵⁴ The Consensus Statement was prepared by “committee members” and a “consultant,” many of whom were paid speakers for Purdue, e.g., J. David Haddox, *see* PKY180955294, *see* _____, Russell K. Portenoy, MD, *see* PKY180357269.

is perceived by healthcare professionals to exhibit behaviors similar to those seen in addiction but is not truly addicted.”⁴⁵⁵

228.2. The sales training document added: the “physician can differentiate addiction from pseudoaddiction by speaking to the patient about his/her pain and increasing the patient’s opioid dose to increase pain relief. Pseudoaddiction behaviors such as clock watching (counting down the time until the next dose) will resolve when the pain is properly treated.”⁴⁵⁶

229. In addition, pain advocacy and professional medical organizations supported by Endo published “educational” materials that recognized pseudoaddiction as a medical condition despite the lack of substantial evidence.⁴⁵⁷ For example, at a 2009 NIPC CME on Chronic Opioid Therapy: Understanding Risk While Minimizing Analgesia, Dr. Perry Fine, a paid speaker,⁴⁵⁸ discussed a hypothetical patient who although instructed not to change her pain treatment plan without consulting her doctor, increased her short-acting opioid. Dr. Fine told an audience of healthcare providers:

We need to understand the definitions of pseudoaddiction and behaviors that may resemble frank abuse or addictive behaviors which, in fact, may be extinguished by good pain control. It is a very important distinction to make.” “The diagnosis is extraordinarily important since addiction is a primary neurobiological disease that is life threatening and needs to be very carefully managed, where pseudoaddiction may reflect a very different issue.” Dr. Fine concluded “In view of this differential diagnosis, Dr. Jones believes that in fact this may represent a combination of tolerance and pseudoaddiction and behaviors that are motivated by pain rather than drug-seeking, per se.”⁴⁵⁹

⁴⁵⁵ ENDO-CHI_LIT-00053284 at 15.

⁴⁵⁶ *Id.* at 16. The sales training module cited to the “AAPM, 2001” for these statements. *Id.*

⁴⁵⁷ See Section XI.

⁴⁵⁸ See, e.g., KP360_OHIOMDL_000037538.

⁴⁵⁹ KP360_OHIOMDL_000121559 at 1, 26.

229.1. Pseudoaddiction was also taught to 3rd and 4th year residents and fellows in Anesthesiology, Neurology, Family Practice, Emergency Medicine and Physical and Rehabilitation Medicine at the APS's Endo-supported "Fundamentals of Pain Management" "intensive two-day course" attended by more than 1,150 residents and fellows.⁴⁶⁰ Specifically, a slide in the 2009 syllabus for the APS's "Fundamentals of Pain Management" stated: "Differential Diagnosis of Aberrant Drug-Taking Attitudes and Behavior" and included "Pseudoaddiction (inadequate analgesia)" as one of five diagnoses along with addiction, chemical copers, other psychiatric diagnosis, and criminal intent."⁴⁶¹

229.2. As late as 2012 NIPC continued to deliver a message of pseudoaddiction to healthcare providers. An NIPC Dinner Dialogue CME entitled Responsible Opioid Prescribing in the Era of REMS,⁴⁶² attended by 486 prescribers from around the country⁴⁶³ including Columbus, Ohio,⁴⁶⁴ presented a clinical case and asked "Although NB had good general pain control with use of his treatment plan, over time, his pain has increased, and he has increased his dosage of medication without permission with no additional benefit. What is the differential diagnosis? 1. Tolerance, 2. Pseudoaddiction, 3. Addiction, 4. Misuse, 5. Abuse, 6. Diversion."⁴⁶⁵

⁴⁶⁰ Linda Kitlinski Deposition, Ex. 41.

⁴⁶¹ ENDO-OPIOID_MDL-05968029 at 38.

⁴⁶² CHI-000929476 at 1.

⁴⁶³ KP360_OHIOMDL_000336756 at 1.

⁴⁶⁴ KP360_OHIOMDL_000336605 at 2.

⁴⁶⁵ ENDO-OR-CID-01252970 at 57; *see also id.* at 58 (pseudoaddiction is defined as "syndrome resulting from undertreatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior. Behavior ceases when adequate pain relief is provided. Not a diagnosis; rather, a description of a clinical interaction.")

230. In my opinion, Endo falsely told healthcare providers that patients exhibiting signs of addiction could be exhibiting “pseudoaddiction” and in need of additional opioids to treat pain.

(d) Endo’s Promotion of Opana ER Minimized the Risks of Respiratory Depression, Addiction and Abuse Associated With Higher Doses

231. Consistent with Purdue’s minimization of the risks associated with higher doses of opioids in its message that OxyContin had no dose ceiling, Endo told healthcare providers that the dose of Opana ER could be adjusted upward without disclosing the potentially fatal risks of respiratory depression and the increased risk of abuse.

231.1. A 2009 Opana ER “Instant Savings” card and Resource Kit told potential Opana ER patients “[s]ome people taking opioids may need to take a higher dose after a period of time in order to have relief from their pain. This is ‘tolerance’ to opioid medications that doesn’t affect everyone who takes them and does **NOT** mean addiction. (Emphasis in original). If tolerance develops, it does not mean you will ‘run out’ of pain relief. Your healthcare provider can adjust your dose or prescribe another medicine.”⁴⁶⁶

231.2. An Endo sponsored brochure entitled Understanding Your Pain: Taking Oral Opioid Analgesics brochure delivered a similar message regarding opioids. In response to the question, “what should I know about opioids and addiction,” the brochure stated: “If tolerance does occur, it does not mean you will ‘run out of’ pain relief. Your dose can be adjusted or another medicine can be prescribed.”⁴⁶⁷

⁴⁶⁶ *Id.*

⁴⁶⁷ ENDO-CHI_LIT-00237187 at 3.

232. In my opinion, Endo's promotion of Opana ER as having no dose ceiling misleadingly minimized the risks of respiratory depression, addiction and abuse associated with higher doses.

(e) Endo Overstated the Benefits of Opana ER With Respect to Work and Functionality

233. Endo did not have adequate and well controlled clinical studies demonstrating that Opana ER improved functionality.

234. Nevertheless, Endo promoted Opana ER as providing pain relief that increases patients' functionality.

234.1. A "Clinical Case Study" featuring a clinical perspective by Gerald M. Aronoff, MD presented a hypothetical patient overview of "Laurie."⁴⁶⁸ Under "Patient Assessment/Diagnosis," it stated "Laurie is an otherwise healthy middle-aged woman presenting with inadequately controlled chronic back pain despite total daily dose of 120 mg OxyContin plus oxycodone/acetaminophen 5 mg/325 mg PRN for supplemental rescue medication. Patient reports difficulty remaining active because of her chronic pain, resulting in a sense of loneliness and isolation."⁴⁶⁹ The "Treatment Goals and Plan" section of the case study stated "[t]he ultimate goal of therapy will be to obtain an appropriate balance between management of pain and suffering, improving daily function, and minimizing opioid-related adverse actions . . . Help Laurie, who may feel isolated and stranded due to her condition, by developing a comprehensive pain management plan . . . Begin OPANA ER (oxymorphone HCl) Extended-Release tablets,

⁴⁶⁸ ENDO-CHI_LIT-00138534 at 3.

⁴⁶⁹ *Id.*

CII, with INTAC technology plus supplemental rescue therapy with OPANA Immediate Release (IR).⁴⁷⁰

234.2. Endo also used hypothetical patient profiles to tout the functionality benefits of Opana ER. In a 2007 “Bill the Patient” profile used with physicians, Endo presented Bill—a “40 year old male construction worker who needs to work to support his family,” with “moderate to severe low back pain treated with pain medication for several months,” and whose “[p]hysician has determined patient is appropriate for continuous around-the-clock opioid therapy.”⁴⁷¹

234.3. In a 2011 patient profile, Endo presented “Frank,” an “[a]uto mechanic whose job requires him to stand on his feet all day,” and who has “been treated for chronic low back pain for 3 years.” The promotional piece continued “[b]ecause Frank is not experiencing adequate pain relief, his physician has been upwardly titrating his dose to increased side effects . . . Frank needs a different long-acting opioid.”⁴⁷²

235. In my opinion, Endo misleadingly overstated the benefits of Opana ER with respect to work and functionality.

3. Endo’s Risk Minimization Action Plan for Opana ER Contained Elements that Understated the Risk Abuse and Addiction and Misleadingly Claimed that Patients Exhibiting Signs of Addiction Were Likely “Pseudoaddicted”

236. To address the risks posed by Opana ER, prior to approval, on October 4, 2001, FDA informed Endo that a risk management program for the drug would be needed at the time of approval.⁴⁷³

⁴⁷⁰ *Id.* at 4.

⁴⁷¹ ENDO-CHI_LIT-00033952.

⁴⁷² ENDO-CHI_LIT-00099937 at 1.

⁴⁷³ ENDO-OPIOID_MDL-00159347 at 4.

236.1. During an August 6, 2003 teleconference between FDA and Endo representatives, FDA “provide[d] Endo with an outline of the essential elements required in a Risk Management Plan (RMP).”⁴⁷⁴ Endo’s minutes of the teleconference reflect that FDA stated: “In general the Agency believes that a RMP should address 3 elements: (1) “Risk of accidental exposure”; (2) “Improper patient selection-how should a physician be selecting patients;” and (3) “Risk for abuse and misuse-how can we reduce risk for patient and community.”⁴⁷⁵

236.2. Consistent with the above, Endo’s former vice president of regulatory affairs, Robert Barto, testified during his deposition that “[a]n agreed-to risk minimization plan with FDA was necessary in order to secure approval for the product.”⁴⁷⁶

237. Endo’s June 2007 Risk Minimization Action Plan for Opana ER made certain representations to FDA including:

237.1. “Endo has developed and is constantly striving to improve a comprehensive ‘Risk Minimization Action Plan (RiskMap) for [Opana ER], which aims to promote the safe and responsible use of the product while concurrently minimizing abuse, misuse, diversion and other adverse events through appropriate drug labeling, tight controls on distribution, proactive pharmacovigilance, extensive education of healthcare professionals and sales personnel, and funding of clinical meaningful research.”⁴⁷⁷

⁴⁷⁴ ENO000087335 at 1.

⁴⁷⁵ *Id.*

⁴⁷⁶ Robert Barto Dep. Tr. (Jan. 30, 2019) 137:3-5, 7-10.

⁴⁷⁷ ENDO-OPIOID_MDL-00290299 at 7.

237.2. Endo represented that its “goals and objectives for this RiskMap are to minimize the following liabilities with opioids class of drugs as it pertains to [Opana ER/IR]” including:

- “Aberrant behavior such as drug abuse, misuse, and addiction” “[a]mong patients” and “[i]n the community, particularly among young adults,”
- “Unintentional drug overdose”
- “Accidental exposure”
- “Diversion from distribution/manufacturing facilities”
- “Improper patient selection”
- “Fraudulent prescription activity”
- “Inadequate patient education”⁴⁷⁸

238. Endo’s RiskMAP for Opana ER also told FDA that it had developed strategies and tools “to minimize the potential risks that may be associated with [Opana ER/IR]” and further represented that “Endo’s RiskMAP is designed to protect the public and help minimize abuse, misuse, and diversion.”⁴⁷⁹

238.1. These “[s]trateg[ies] and [t]ools” included Product Labeling, Education consisting of “Professional Education Initiatives” such as continuing medical education (“CME”) presented by various educational media such as: National Initiative on Pain Control (“NIPC”) Dinner Dialogue Programs, audioconferences, half-day symposia, newsletters and webcasts, thePainEdu.org website and manual,⁴⁸⁰ the AAPM/APS

⁴⁷⁸ EPI000750019 at 8; Robert Barto Dep. Tr. (1/30/2019) 140:7-13, 21-141:7, 142:20-143:2 (“Endo worked with FDA to establish these goals and objectives, and these were the agreed-to goals and objectives with FDA as part of this RiskMAP.”)

⁴⁷⁹ *Id.* at 8-9.

⁴⁸⁰ According to the Opana ER RiskMAP, *PainEdu* “makes use of case-based learning, roundtable discussions, ‘ask the expert’ modules, downloadable tools such as SOAPP, an electronic download of the Clinical Companion

Consensus Statement on the Use of Opioids for the Treatment of Chronic Pain, and the Pain Action website, among other components.⁴⁸¹

238.2. Bob Barto, Endo's Vice President of Regulatory Affairs, likewise confirmed during deposition testimony that "education" including National Initiative on Pain Control programming, www.PainEdu.org, AAPM/APS, Pain Action, and oversight of the distribution chain were part of the risk minimization plan for Opana ER.⁴⁸²

239. As discussed below, Endo's RiskMap for Opana ER contained elements that understated the risk of abuse and addiction and misleadingly claimed that patients exhibiting signs of addiction were likely "pseudoaddicted."

(a) Elements of the "Professional Education Initiatives" in the Opana ER RiskMap Falsely Told Healthcare Providers that Patients Exhibiting Signs of Addiction Could Be Exhibiting "Pseudoaddiction" and in Need of Additional Opioids to Treat Pain

240. Despite Endo's representation to FDA that its RiskMAP for Opana ER was designed to address the risks of Opana, components of the Professional Education Initiatives in the Opana ER RiskMap taught healthcare providers the concept of pseudoaddiction—the unsubstantiated claim that signs of drug seeking are pseudoaddiction rather than addiction and require more opioids to resolve.⁴⁸³

manual and makes use of varied educational strategies." *Id.* at 16. Endo funded the "development, maintenance and continued enhancement of *PainEdu*." *Id.*

⁴⁸¹ *Id.* at 2.

⁴⁸² Barto Depo Tr. 143:21-144:14; 146:19-22. Mr. Barto suggested that the RiskMAP "didn't work." *See* Barto Depo Tr. 244:20-24 ("If the RiskMap didn't work and communicating to healthcare providers didn't work, then moving to another system might have similar challenges in being effective. I thought maybe a different tact to go directly to the public would be of benefit.")

⁴⁸³ *See* discussion of pseudoaddiction in Purdue section.

240.1. Between October 26, 2006 through December 12, 2006, NIPC hosted a Dinner Dialogues Series entitled “Advances in Opioid Analgesia: Maximizing Benefit While Minimizing Risk” held in cities around the United States. Endo described the program as one that “specifically, address[ed] the responsible prescribing of opioid analgesics.”⁴⁸⁴

240.2. A slide in the presentation entitled “Advances in Opioid Analgesia: Maximizing Benefit While Minimizing Risk” described “Pseudoaddiction” as a “Pattern of drug-seeking behavior of patients with pain receiving inadequate pain management that can be mistaken for addiction” and identified purported signs of pseudoaddiction such as “concerns about availability,” “clock watching,” and unsanctioned dose escalation.” The slide stated that “pseudoaddiction” may “resolve with reestablishment of adequate analgesia or adjustment of analgesic dose/schedule.”⁴⁸⁵

240.3. An NIPC Dinner Dialogue CME entitled Responsible Opioid Prescribing in the Era of REMS,⁴⁸⁶ attended by 486 prescribers from around the country⁴⁸⁷ including Columbus, Ohio,⁴⁸⁸ presented a clinical case and asked “Although NB had good general pain control with use of his treatment plan, over time, his pain has increased, and he has increased his dosage of medication without permission with no additional benefit. What

⁴⁸⁴ EPI000750019 at 11.

⁴⁸⁵ ENDO-CHI-LIT-00544711 at 6.

⁴⁸⁶ CHI-000929476 at 1.

⁴⁸⁷ KP360_OHIOMDL_000336756 at 1.

⁴⁸⁸ KP360_OHIOMDL_000337097.

is the differential diagnosis? 1. Tolerance, 2. Pseudoaddiction, 3. Addiction, 4. Misuse, 5. Abuse, 6. Diversion.”⁴⁸⁹

240.4. An NIPC audioconference series entitled “Advanced in Opioid Analgesia, Maximizing Benefit While Minimizing Risk” presented by Dr. B. Elliott Cole instructed a group of 50 healthcare providers: “pseudoaddiction is . . . clock watching behavior . . . that suggests . . . they’re not getting enough medication and often what fixes their aberrant behavior is a dose increase to the point where they become comfortable.”⁴⁹⁰

240.5. The Pain.edu website and Manual similarly downplayed concerns about addiction by claiming a distinction between pseudoaddiction and addiction. The Manual for Painedu.org under the topic “Prescribing Considerations” stated: “Two major considerations are important when prescribing opioids: the *fear of regulatory and legal scrutiny* and the *fear of addiction*, which can ultimately contribute to the undertreatment of pain. Fears of sanctions by regulatory agencies are largely exaggerated . . . Another fear that leads to the undertreatment of pain with opioids is addiction. It is important that the clinicians understand and be able to convey to the patient and family, the distinction between physical dependence, addiction and pseudoaddiction . . . *Pseudoaddiction* is a term used to describe behavior that appears to be addictive, ‘drug seeking’ behavior but is actually an effort to obtain pain relief by a nonaddicted patient who is not receiving adequate analgesia.”⁴⁹¹

⁴⁸⁹ ENDO-OR-CID-01252970 at 57; *see also id.* at 58 (pseudoaddiction is defined as “syndrome resulting from undertreatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior. Behavior ceases when adequate pain relief is provided. Not a diagnosis; rather, a description of a clinical interaction.”)

⁴⁹⁰ KP360_OHIOMDL_000017045 (transcribed) (56:35-56:61).

⁴⁹¹ END00051444 at 127-28, 131.

240.6. *A clinical guide to Opioid Analgesia* authored by Russell Portenoy, MD and Perry Fine, MD⁴⁹² under the heading “Pseudoaddiction” stated: “Pseudoaddiction refers to the development of abuselike behaviors that are driven by desperation surrounding unrelieved pain and are eliminated by measures that relieve the pain, such as increase in medication dose.”⁴⁹³

241. In my opinion, the above referenced components of the “Professional Education Initiatives” in the Opana ER Riskmap falsely told healthcare providers that patients exhibiting signs of addiction could be exhibiting “pseudoaddiction” and in need of additional opioids to treat pain.

(b) Elements of the “Professional Education Initiatives” in the Opana ER RiskMap Minimized the Risk of Addiction Associated with Opioids

242. Notwithstanding Endo’s representation to FDA that its RiskMAP for Opana ER was designed to address the risks of Opana, components of the Professional Education Initiatives in the Opana ER RiskMap minimized the risk of addiction associated with opioids and Opana ER.

242.1. The “AAPM/APS ‘Consensus Statement on the Use of Opioids for the Treatment of Chronic Pain’” a component of the Opana ER Risk Map stated: “Misunderstanding of addiction and mislabeling of patients as addicts result in unnecessary withholding of opioid medications.” The Consensus Statement also misrepresented the rate of addiction stating,

⁴⁹² According to Endo’s RiskMAP, Endo distributed hardcopies of the book since mid-2004 and during 2005, an electronic version was posted to www.stoppain.com website. EPI000750035 at 17. In addition, copies of the book were mailed to participants in the NIPC’s Conference Line Series entitled: Advances in Opioid Analgesia: Maximizing Benefit While Minimizing Risk. *See, e.g.*, KP360_OHIOMDL_000052615.

⁴⁹³ ENDO_OPIOID_MDL-03862731 at 88.

“[s]tudies indicate that the de novo development of addiction when opioids are used for the relief of pain is low.”⁴⁹⁴

242.2. *A clinical guide to Opioid Analgesia* authored by Russell Portenoy, MD and Perry Fine, MD likewise downplayed the risk of addiction with opioids. Under the heading “Risk of Addiction,” it stated: “Overall, the literature provides evidence that the outcomes of drug abuse and addiction are rare among patients who receive opioids for a short period (ie, for acute pain) and among those with no history of abuse who receive long-term therapy for medical indications. The risk should not be assumed to be nil, however, and it may vary with specific characteristics of the patient.”⁴⁹⁵

243. In my opinion, Endo through its distribution of the AAPM/APS ‘Consensus Statement on the Use of Opioids for the Treatment of Chronic Pain’ and *A clinical guide to Opioid Analgesia* as part of the Opana ER Riskmap minimized the risk of addiction associated with Opana ER and opioids in general.⁴⁹⁶

⁴⁹⁴ This statement is also inconsistent with the launch label for Opana ER. At FDA’s request, Endo deleted similar language from the Opana ER label. *See* ENDO-OPIOID_MDL-00299009 at 1-2 (striking “[t]he development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients” from the label).

⁴⁹⁵ ENDO_OPIOID_MDL-03862731 at 40.

⁴⁹⁶ In addition to “Professional Education Initiatives,” Endo’s RiskMap for Opana ER represented to FDA that for “all of Endo’s controlled substance products, the manufacturing and distribution chain highly controlled and closely monitored.” EPI000750019 at 23. Endo further represented that its “oversight includes physical and administrative controls as well as significant monitoring activities.” *Id.* With regard to “Excessive Orders Management,” Endo told FDA that it flagged all orders as “excessive” for additional review if: (1) “the order exceeded the past 3 months average shipped quantity,” and /or (2) the order exceeded the past 12 months average shipped quantity by 15%. *Id.* at 43 (Appendix 3 to Opana ER Riskmap-Order Processing and Distribution). Endo’s Director of Customer Service and Distribution, Lisa Walker, confirmed the inadequacy of Endo’s oversight of the distribution chain. During her deposition, in response to the question whether “Endo ever reported suspicious orders for one of its branded products to DEA,” Ms. Walker testified “No, we have not.” Lisa Walker Depo Tr. 55:5-7, 10-11.

4. Endo's Promotion and Sales of Opana ER Increased as Reports of Abuse Grew.

244. During the five years that Endo promoted Opana ER, Endo increased its marketing expenditures by \$111,282,686⁴⁹⁷ with sales increasing from \$66,306,804 to \$1,028,255,461.⁴⁹⁸

245. As prescriptions and sales of Opana ER increased, Endo received increasing reports of abuse Opana ER abuse.

246. In as early as 2009, Endo received reports documenting addiction and abuse with Opana ER with reports increasing over time.

246.1. A March 23, 2009 email from Frank Yuen Clinical Affairs Manager regarding www.wate.com: Newport police: abuse of prescription drug Opana on the rise stated: "On Saturday I attended a Beth Israel Medical Center (New York) conference entitled: 'Emerging Practices in Opioid Prescribing for Chronic Pain.' During the morning Q & A session, a physician (Joe Browder, MD-Tennessee) . . . mentioned the 5 'Opana' deaths in Tennessee in recent times . . . He told me that all of the deaths were related to recreational use. One death was the result of an opioid naïve 18 year old getting hold of a relative's Opana and crushing it and snorting it . . . He also believed that the severe restrictions on OxyContin may have contributed to the experimentation with Opana. Dr. Browder said to the audience that his county was among those with the

⁴⁹⁷ END00000923 at slides 56-57 (2006 Opana Business Plan); EPI000560276 at slide 58 (2008-2012 Opana Brand Tactical Plan); EPI001474537 at slide 13 (Branded Pharmaceuticals Budget Overview); ENDO-CHI_LIT-00439415 at 53 (Branded Pharmaceuticals Business Review).

⁴⁹⁸ Endo sold Opana ER for part of 2012 and had sales of \$74,842,095.

highest incidence of OxyContin abuse in the country. Brian's name was not mentioned as a possible link to this *epidemic*.”⁴⁹⁹

246.2. A May 1, 2009 email from Heidi Higgins, Special District Manager for Endo, to John Doyle, Corporate Compliance and Business Practices Director for Endo regarding “Reports of Opana Abuse in the state of Ohio—Dr. Miles” sent with an importance level of “High” forwarded an OSAM-O-GRAM dated June 2008-January 2009, a document containing “key findings of the Ohio Substance Abuse Monitoring (OSAM) Network.” The document stated: “[u]sers in Athens and Cincinnati indicated that the Opana ‘high’ was comparable to or even better than that of OxyContin (oxycodone, extended release). A white female user in her 20s from Athens reported that her best friend had obtained a tablet illegally and inhaled it intranasally. She commented ‘And I guess you can really blow out of it, for less [than a tablet of OxyContin].’ Another white female in her mid-20s added, ‘*Right, I guess that’s like an Oxy times 10 . . .*’ A 30 year-old white female user from the Cincinnati region who was being treated for prescription opioid abuse stated that, ‘The oxymorphone is the best . . . even better than oxycodone. I can do a whole Oxy 80 [80 milligram strength tablet of OxyContin] and nothing happens, but if I take one of them pills [Opana ER] I can get a buzz; . . . that’s how I get the energy to do things around the *house*.”⁵⁰⁰

246.3. A May 1, 2011 Drug Enforcement Administration Drug Intelligence Briefing for the Philadelphia stated “[t]he Philadelphia Division Intelligence Program received information on a possible emerging trend in the region; Oxymorphone (brand name Opana) has been reported by several sources of information as the ‘big thing right

⁴⁹⁹ END00361409.

⁵⁰⁰ ENDO-OPIOID_MDL-02178254 at 3.

now’ in pharmaceutical drug abuse in the region.” The Brief further noted “[s]lang terms for oxymorphone include: blues, biscuits, blue heaven, new blues (although the immediate-release tablets are pink and off-white), octagons (extended-release), [strength], octagons, stop signs, pink, pink heaven . . . pink heaven, pink lady, Mrs O, OM, Pink O, The O Bomb . . . and others.”⁵⁰¹

246.4. On August 16, 2011, Geoffrey Becker sent Timothy Byrne, senior director of public policy at Endo and colleagues an article from the Charleston WV Daily Mail entitled “Crushable pain medication a target for abusers.” The article stated: “Authorities are finding more people abusing prescription Opana, a drug that appeared on officers’ radars after OxyContin was reformulated late last year, said Charleston Lt. Chad Napier.” The article further stated “[t]he use of Opana started slowly climbing because Purdue Pharma was getting such bad press with the asset forfeitures and abuse statistics.”⁵⁰²

247. At the same time, Endo failed to use available information to detect unusual prescribing patterns that could indicate abuse or diversion of the drug.

247.1. A February 9, 2012 email from Alicia Logan, Brand Manager at Endo, to Javier Avalos, Senior Director of Channel Strategy in Endo’s Trade Group, included a list of “Pharmacies that stated REFUSAL-PRESCRIBING PHYSICIAN as a Decline Reason.”⁵⁰³

⁵⁰¹ ENDO-OR-CID-00694084.

⁵⁰² EPI000987149.

⁵⁰³ ENDO-OPIOID_MDL-00468003 at 1-2.

247.2. Included on the list of physicians for whom pharmacies refused to fill prescriptions was Dr. Oliver Herndon.⁵⁰⁴

247.3. According to a news report distributed internally at Endo, “Dr. Herndon prescribed Opana and other potent narcotics based on three-minute office visits devoid of physical examinations or case histories.”⁵⁰⁵

247.4. Despite the availability of information stating that pharmacies were refusing to fill prescriptions by Dr. Herndon to Endo’s trade group, Endo’s Vice President of Sales, Larry Romaine, testified at his deposition that he did not recall being aware that such information existed.⁵⁰⁶

247.5. Dr. Herndon, “the #1 prescriber of [Opana ER] in the nation” who was on Endo sales reps’ call list since at least 2010,⁵⁰⁷ remained on that list until November 2012 when he was removed because of “no access”⁵⁰⁸ after he pled guilty to healthcare fraud and improper distribution of oxycodone and oxymorphone.⁵⁰⁹

⁵⁰⁴ *Id.*

⁵⁰⁵ *Id.*

⁵⁰⁶ Larry Romaine Depo Tr. 217:3-15.

⁵⁰⁷ Larry Romaine Depo Tr. 381:23-382:3 (“Dr. Herndon ha[d] been detailed since at least 2010” as part of Endo’s “library program.”); *see also* ENDO-OPIOID_MDL-00817302 at 141.

⁵⁰⁸ ENDO-OPIOID_MDL-02924490 at 65.

⁵⁰⁹ ENDO-OPIOID_MDL-02314929 (June 18, 2012 email from Janett Mendez DeTore, Endo Region Business Director to Larry Romaine, Endo Vice President of Sales, forwarding Pittsburgh post-gazette.com news article with the same date reporting that Dr. Oliver W. Herndon had “pleaded guilty last month to health care fraud and improper distribution of oxycodone and oxymorphone.”).

248. Endo also received reports of healthcare provider prescribing levels for Opana ER, but based on testimony provided, did not use this information to look for unusual prescribing patterns that could indicate abuse or diversion of the drug.⁵¹⁰

248.1. Larry Romaine, Endo's Vice President of Sales, testified that "at any given period for a given product," information regarding which prescribers were prescribing the most product was available to him.⁵¹¹ Mr. Romaine agreed that such data could be looked at for "patterns of prescribing for individual doctors" including "whether that doctor's prescriptions were fairly high compared to other prescribers in any given territory."⁵¹²

248.2. Neither Mr. Romaine nor Brian Lortie, Endo's Senior Vice President and General Manager for Branded Pharmaceuticals,⁵¹³ however, could recall that such data was used to detect suspicious prescribing activity.⁵¹⁴

248.3. Mr. Lortie testified that "Endo certainly had policies and procedures to . . . measure prescriptions for its products" but could not "recall specifically" the "extent that that was used as part of an abuse and diversion mitigation process."⁵¹⁵

⁵¹⁰ The opioid manufacturers were in possession of detailed prescription data that included product information, such as dosage, number of units prescribed, the prescriber, geographic location of the prescriber and pharmacy, and method of payment. *See, e.g.*, PDD1502500909; E1247_ENDO-OPIOID_MDL-02924490; ACTAVIS0723709; JAN00114751; MNK-T1_0000106040.

⁵¹¹ Larry Romaine Depo Tr. 293:24-294:14.

⁵¹² *Id.* at 301:2-5, 8-13, 301:15-19-302:1.

⁵¹³ Brian Lortie Depo Tr. 28:19-24.

⁵¹⁴ Larry Romaine Depo Tr. at 303:18-304:4, 6-11, 304:22-305:6, 8.

⁵¹⁵ Brian Lortie Depo Tr. 159:12-19.

248.4. When asked to confirm that “it was not anyone’s specific job to proactively monitor . . . on a monthly basis sales data to see if it could detect any unusual patterns that may be indicative of a pill mill,” Mr. Lortie testified, he was “not sure.”⁵¹⁶

248.5. Mr. Lortie further testified that Endo “absolutely” did not “have a policy as part of its anti-diversion efforts by which sales reps were to actively go out and ask healthcare providers they were calling on whether those healthcare providers had suspicions about any pill mills that may exist in a territory that the sales rep served,” because the sales reps were not “law enforcement agents.”⁵¹⁷

248.6. Mr. Lortie was also unaware that Endo conducted “any due diligence . . . to see whether [a] healthcare provider might, in fact, be a pill mill” before adding a physician to a call list.⁵¹⁸

249. By 2012, Endo received reports that according to the Ohio’s Substance Abuse Monitoring Network “Opana was becoming popular as a replacement for OxyContin [in Akron, Cincinnati and Athens, Ohio] as it was easier to use.”⁵¹⁹ The report also noted that Opana 40 mg tablets had eclipsed street prices for OxyContin.⁵²⁰

250. That same year, Endo acknowledged its “contribution” to the opioid crisis:

250.1. At a 2012 Pain Management Summit, Neil Shusterman, Endo’s Director of Pharmacovigilance, stated: “[T]he old Opana was very, very easy to crush. Anybody in this room could easily do it by just taking their [fist] and reducing it to a powder on a

⁵¹⁶ *Id.* at 11-17, 20-21.

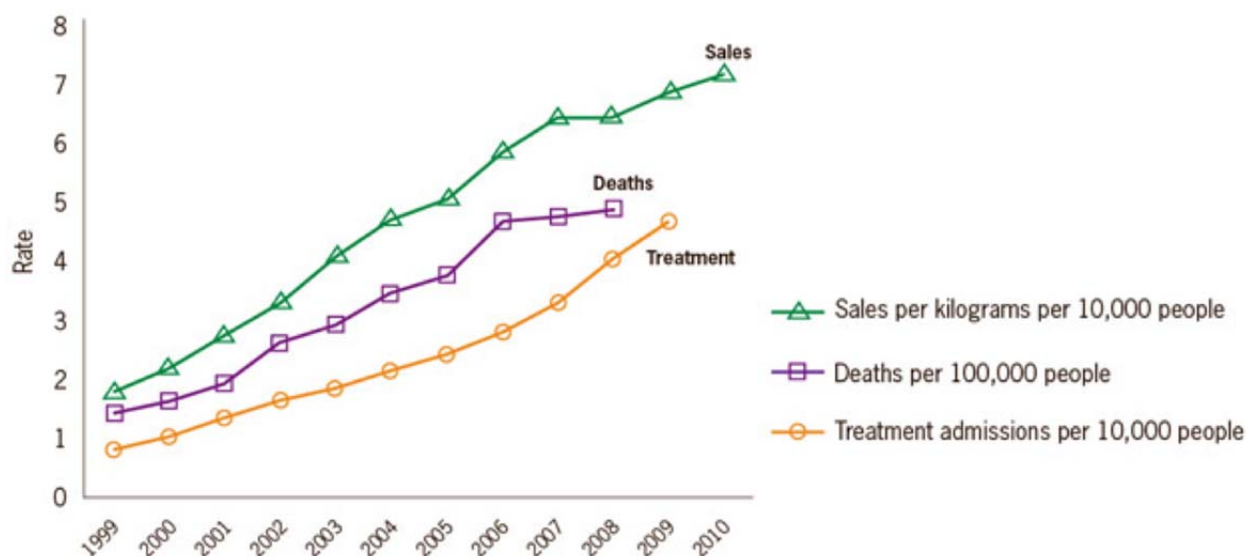
⁵¹⁷ *Id.* at 164:24-165:1-6, 8-12.

⁵¹⁸ *Id.* at 169:6-12, 14-19.

⁵¹⁹ EPI000832250.

⁵²⁰ *Id.*

tabletop. And therein lay the problem as I'll get to because nasal insufflation, snorting was the major route of abuse with Opana. And we felt therefore we needed to come up with a technology that would make it harder."⁵²¹ Referring to a chart from the National Vital Statistics System on Rates of Prescription Pain Killer Sales, Deaths and Substance Abuse Treatment Admissions from 1999-2010,⁵²² Mr. Shusterman stated "Everybody's seen this slide. I don't see how any of these talks can start without showing the magnitude of the problem. And we felt that being responsible to what we knew to be our specific contribution to the problem was the right thing to do."⁵²³



251. In my opinion, Endo's promotion and sales of Opana ER increased as reports of abuse grew.

⁵²¹ END00649416 at 167.

⁵²² END00648960 at 38. Mr. Shusterman's slide deck contains a black and white version of the above chart. For improved readability, a color version of the same chart obtained from <https://www.cdc.gov/vitalsigns/painkilleroverdoses/> (the same source noted on Mr. Shusterman's slide) is included above.

⁵²³ *Id* at 168.; END00648960 at 38.

D. Opana ER Reformulated

1. Endo's Marketing Strategy for Opana ER Reformulated

252. An important purpose in developing Opana ER reformulated was to replace Opana ER original, which would face generic competition. As described in a 2007 Endo document, “a TRF formulation of ER will be important to secure” “[t]o ensure we continue to protect the franchise in the face of loss of regulatory exclusivity in 2009 . . . Without this LCM strategy, Opana ER is expected to lose about 70% of its sales within six months if generic entry occurs.”⁵²⁴

253. A distinction between the reformulated Opana and the original formulation was that it was made with Intac technology. Intac technology, developed by Grunenthal GmbH, is “[a] manufacturing process that [combines] an active drug (oxymorphone HCl) with a [polyethylene oxide (PEO)] of high molecular weight above the PEO melting point and simultaneously [applies] force on the heated mass.”⁵²⁵

2. FDA Denial of Abuse Deterrent Claim as to Opana ER Reformulated

254. Endo sought to obtain approval of Opana ER reformulated with abuse-deterrent labeling claims.⁵²⁶

254.1. During Pre-IND Meetings with FDA, Endo learned that “[n]o claims of abuse deterrence or resistance will be allowed based on tablet hardness.”⁵²⁷

254.2. Early on in the development of the reformulated drug, initial testing of the reformulated opioid supported the conclusion that “TRF can be overcome with additional

⁵²⁴ ENDO-CHI_LIT-00176743 at 1.

⁵²⁵ ENDO-CHI_LIT-00227354 at 9.

⁵²⁶ See ENDO-OR-CID-01174358 at 1-3.

⁵²⁷ ENDO-CHI_LIT-00020555 at 3.

time, effort, and money” and “[p]ossible weaknesses” included “i.v. and tablet heated in liquid.”⁵²⁸

254.3. On December 27, 2010, FDA removed a description of the physiochemical properties from the proposed label of Opana ER reformulated because FDA “felt the text suggests an impermeability to manipulation which the Division doesn’t believe is the case.”⁵²⁹

254.4. On January 4, 2011, based on the FDA’s review of Endo’s studies for Opana ER Reformulated, FDA provided Endo with its preliminary conclusion that an abuse-deterrent labeling claim was not warranted, stating “[Opana ER] provides limited resistance to physical and chemical manipulation for abuse. Revopan’s extended-release mechanism can be overcome by cutting, chewing, or grinding . . . [Opana ER reformulated] tablets provide some resistance to crushing using simple tools such as two spoons, a pill crusher or hammer.”

254.5. In this letter, FDA also stated that “[t]he product label should not include language asserting that [Opana ER] provides resistance to crushing, because it may provide a false sense of security since the product may be chewed and ground for subsequent abuse.”⁵³⁰

255. After receiving the January 4, 2011 letter from FDA, Endo amended its NDA for Opana ER and to remove its request for approval of an abuse deterrent labeling claim.”⁵³¹

⁵²⁸ ENDO-CHI_LIT-00064407 at 6.

⁵²⁹ EPI001313732 at 2.

⁵³⁰ *Id.* at 2- 3.

⁵³¹ Endo later again sought approval of an abuse deterrent labeling claim for Opana ER Reformulated but did not receive FDA approval for such a claim.”

**3. Endo Marketed Opana ER Reformulated as “Crush Resistant”
Despite FDA’s Instruction Otherwise**

256. Endo’s launch materials included claims regarding the physiochemical properties of Opana ER reformulated suggesting that the reformulation was safer than the old version. FDA took issue with these launch materials. Specifically, in an April 30, 2012 letter from Samuel M. Skariah, Regulatory Review Officer in the Division of Drug Promotion (“DPDP”) Office of Drug Promotion at FDA to William A. Best, Sr., Director Promotional Regulatory Affairs raised concerns that Endo’s promotional launch materials for Opana ER Reformulated suggested a therapeutic advantage not supported by substantial evidence.⁵³² The letter from DPDP stated:

256.1. “The proposed detail aid contains numerous claims and presentations describing Opana ER’s new formulation and its INTAC™ technology . . . the totality of [which] suggest that, as a result of its new formulation Opana ER offers a therapeutic advantage over the original formulation when this has not been demonstrated by substantial evidence or substantial clinical experience.”

256.2. “For example, page two includes claims such as the following: ‘**INTAC™ technology provides mechanical stability,**’ ‘Innovative manufacturing process uses heat extrusion to create mechanical strength’ (page 2); ‘New formulation of Opana ER tablets with INTAC technology has the mechanical; strength to provide an obstacle to crushing by tools, including hammers, spoons, and mechanical pill crushers’”

256.3. “Additionally, page three includes claims and presentations such as the following regarding a blinded comparative study in 25 subjects (bolded emphasis in original: ‘**Opana ER with INTAC™ technology compared to oxymorphone ER**

⁵³² ENDO-CHI_LIT-00015924

(original formulation) . . . Provided some resistance to crushing by tools, including spoons, a hammer, or a razor”

256.4. “**Manipulating Opana ER tablets with INTAC™ technology resulted in larger particle size than oxymorphone ER** (original formulation)’ (with accompanying visual); ‘Study demonstrated the difficulty in forming an intranasal preparation’ (with accompanying visuals)”

256.5. FDA’s letter clarified that statements such as “[t]he clinical significance of INTAC technology or its impact on abuse/misuse has not been established for the new formulation of Opana ER’ on various pages of the piece” did “not mitigate the overwhelming misleading impression” of the detail aid.

256.6. Finally, FDA advised: “[w]e are especially concerned from a public health perspective because the presence of this information in the detail aid could result in health care practitioners or patients thinking that the new formulation is safer than the old formulation, when this is not the case.”⁵³³

257. Despite FDA’s letter concerning Endo’s launch materials for Opana ER reformulated, Endo agreed on a promotional strategy for Opana ER reformulated on May 15, 2012 that included the phrase “Designed to be crush resistant,” acknowledging that this strategy risked a warning letter from FDA.⁵³⁴

258. Endo also trained its sales reps to promote Opana ER Reformulated as designed to be crush resistant. For example, a May 2012 sales training aid stated:

⁵³³ *Id.* at 2.

⁵³⁴ ENDO-OR-CID-00345837 at 1; A December 12, 2011 press release announcing FDA approval of Opana ER Reformulated stated: “Endo Announces FDA Approval of a New Formulation of Opana ER Designed To Be Crush-Resistant.” ENDO-CHI_LIT-00002025 at 1.

The **ONLY approved** message that you can proactively communicate with your HCPs regarding the INTAC Technology is: “INTAC Technology is designed to be crush resistant. However, the clinical significance of INTAC Technology or its impact on abuse/misuse has not been established for Opana ER. Opana ER has an abuse liability similar to other opioid analgesics as stated in the boxed warning.”⁵³⁵

259. By 2013, Endo’s message that Opana Reformulated was “crush resistant” had been delivered to healthcare providers:

259.1. A June 7, 2013 Opana ER with INTAC 2013 Research Report reported the following regarding healthcare providers “Perception and Usage of [Opana ER Reformulated]: “Many HCPs express concern about patient safety. They feel Opana ER is superior to oxymorphone HCI ER because of its crush-resistant formula. They would prefer to use Opana ER, if possible.” The Report also stated that “Some HCPs recall hearing” that Opana ER is “Crush-resistant/tamper proof” with one physician reporting that “[t]hey’ve told me it’s designed to be crush-resistant and that is a big deal. I want all of my patients to [] have as little potential for abuse as possible.”⁵³⁶

259.2. A slide entitled “Perception and Usage of Opana ER” in an Opana ER with INTAC 2013 Research Q2 Qualitative Research Report dated June 7, 2013 stated: “Some HCPs recall hearing the following information recently about Opana ER (2+ mentions)”: Crush-resistant/tamper-proof.”⁵³⁷

259.3. Endo likewise promoted and positioned Opana ER Reformulated to Compendia. As described in a December 2012 Compendia status update from “[a]ll 3 Data Compendia have uniquely classified Opana ER with INTAC technology based on the dosage form of Crush Resistant . . . With a unique classification, Opana ER

⁵³⁵ ENDO-CHI_LIT-00271332 at 1.

⁵³⁶ END00591813 at 9-10.

⁵³⁷ END00591813 at 10.

prescriptions have a much lower probability of being switched at the pharmacy with non-CRF generic formulation.”⁵³⁸

260. In my opinion, Endo marketed Opana ER as “Crush Resistant” despite FDA’s instruction otherwise.⁵³⁹

4. Despite Increasing Evidence of Abuse of Opana ER Reformulated, Endo Continued to Promote Opana ER Reformulated in the Manner Described Above and Thus Put the Public Health At Risk.⁵⁴⁰

261. In 2012 and 2013, sales of Opana ER Reformulated increased from \$221,550,787 to \$222,796,458⁵⁴¹.

262. As prescriptions of Opana ER Reformulated increased, Endo received increasing reports of abuse.

262.1. A November 19, 2012 NAVIPRO Addiction Vigilance Intervention and Prevention Program Report stated “Review of data from the ASI-MV indicated that during Q3 2012, past 30-day abuse of reformulated Opana ER was reported at a level comparable to that of the original version of the product and most frequently via oral ingestion (i.e., by swallowing the tablet whole) and injection . . . These initial observations from NAVIPPRO during this transition period suggest that the reformulated product may have a different abuse profile than the original formulation.”⁵⁴²

⁵³⁸ EPI002485011 at 4, 6. Endo discontinued use of “designed to be crush resistant” claim after denial of Citizen Petition. (Kristin Vitanza Depo Tr. 481:2-8, 17-22)

⁵³⁹ See also EPI002485011 at 4. (Endo Compendia Status Updated stated “[a]ll 3 Data Compendia have uniquely classified Opana ER with INTAC technology based on the dosage form of Crush Resistant.”)

⁵⁴⁰ Endo discontinued the promotion of Opana ER Reformulated as “designed to be crush-resistant” as of May 2013. See END00126255 at 3; see also Kristin Vitanza Depo. Tr. 481:2-8, 11-22 (Endo discontinued use of “designed to be crush resistant” claim in promotion of Opana ER Reformulated after FDA’s denial of Endo’s citizen petition).

⁵⁴¹ ENDO_DATA-OPIOID_MDL-00000014; ENDO-DATA-OPIOID_MDL-00000016.

⁵⁴² ENDO-OR-CID-00829694 at 9.

262.2. A February 5, 2013 NAVIPPRO Epidemiology Programs Study Report stated “reports of abuse of the reformulation via alternate routes of administration (i.e., particularly injection) continue to be observed.”⁵⁴³

262.3. In a May 10, 2013 response to a supplemental new drug application submitted by Endo seeking an abuse deterrent labeling claim, FDA stated that postmarketing data was insufficient “to support any conclusion about the overall or route-specific rates of abuse of Opana ER.” However, FDA noted “if the early trends in postmarketing data . . . are supported by data from further assessments, it would appear that a reduction in abuse by insufflation may be accompanied by a rise in intravenous abuse. This would be a transition to a more dangerous behavior, as intravenous abuse is associated with a greater risk of infection, including hepatitis, HIV and bacterial pathogens, along with a greater risk for overdose and death.”⁵⁴⁴

262.4. On March 13-14, 2017, the majority of a Risk Management Advisory Committee and the Anesthetic and Analgesia Drug Products Advisory Committee Joint Meeting voted “No,” “indicating their belief that the benefits of reformulated Opana ER do not continue to outweigh its risks.”⁵⁴⁵

262.5. On June 8, 2017 FDA advised Endo “it believes the benefits of reformulated Opana ER no longer outweigh the risks that accompany the product,

⁵⁴³ ENDO-OPIOID_MDL-00350952 at 28.

⁵⁴⁴ ENDO-OR-CID-01174358 at 2.

⁵⁴⁵ Summary Minutes of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesia Drug Products Advisory Committee Joint Meeting Mar. 13-14, 2017 available at: <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM551226.pdf> (last visited Mar. 12, 2019).

therefore Endo should voluntarily cease marketing Opana ER.”⁵⁴⁶ During the meeting, “Endo agreed to stop manufacturing of the drug product immediately and cease shipping by August 31, 2017.”⁵⁴⁷

263. In my opinion, despite increasing evidence of abuse of Opana ER Reformulated, Endo continued to promote Opana ER Reformulated in the manner described above and thus put the public health at risk.⁵⁴⁸

VII. JANSSEN

A. Overview

264. Janssen has promoted and sold opioid products known as Duragesic, Nucynta IR, and Nucynta ER.

265. As set forth below, Janssen contributed to the change in the practice of medicine with regards to pain treatment, and the concomitant expansion of both the use and abuse of opioids, by misleading promotion and marketing that minimized the risks and overstated the benefits of its opioid drugs.

⁵⁴⁶ ENDO-OPIOID_MDL-01831503 at 3. As discussed above, information available to Endo in 2009 indicated that injection was another potential route of abuse for Opana ER Reformulated. *See* ENDO-CHI_LIT-00064407; ENDO-CHI_LIT-0006790118.

⁵⁴⁷ *Id.* at 4. Weeks before the withdrawal, Endo offered wholesaler customers 20% off their purchases of the soon-to-be withdrawn drug. *See* ENDO-OPIOID_MDL-02290107 at 1-2 (approving of Opana ER Wholesaler Promotion).

⁵⁴⁸ Endo took some steps to address reports of abuse, but they were limited. *See, e.g.*, EPI000727600 at 3 (public service announcement in 97 movie theatres in Tennessee beginning on March 1, 2013); ENDO-OR-CID-00969795 (educational materials distributed to healthcare providers in Tennessee).

B. Duragesic

1. Regulatory Background

(a) Relevant labeling history

266. Duragesic is a fentanyl transdermal patch manufactured and marketed by Janssen. The patch provides continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours.⁵⁴⁹

267. Duragesic was first approved in August 1990 for “the management of chronic pain in patients requiring opioid analgesia.”⁵⁵⁰ The indication stated that Duragesic was not recommended in the management of postoperative pain.⁵⁵¹ The label also carried the precaution that all doses except the lowest Duragesic dose, 25 µg/h, “are too high for initiation of therapy in non opioid-tolerant patients and should not be used to begin Duragesic therapy in these patients.”⁵⁵²

268. In January 1994 the indication in the label was updated to “the management of chronic pain in patients who require *continuous* opioid analgesia for pain *that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids.*”⁵⁵³

269. A statement that Duragesic is contraindicated in the management of acute or post-operative pain was added to the contraindications section by 1998, as was a statement that Duragesic was contraindicated in “the management of mild or intermittent pain that can otherwise be managed by lesser means such as acetaminophen-opioid combinations, non-

⁵⁴⁹ JAN-MS-00238727.

⁵⁵⁰ JAN-MS-00238727; JAN-MS-00551711.

⁵⁵¹ JAN-MS-00238727.

⁵⁵² JAN-MS-00238727.

⁵⁵³ JAN00221820 at 32 (emphasis added for significant changes).

steroidal analgesics, or PRN dosing with short-acting opioids.”⁵⁵⁴ The label was also updated by this time to state that Duragesic was contraindicated “in doses exceeding 25 µg/h at the initiation of opioid therapy.”⁵⁵⁵

270. In February 2005, the indication changed again to “management of *persistent, moderate to severe* chronic pain that cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate release opioids.”^{556 557}

271. In 2005, a black box warning was added stating **“FOR USE IN OPIOID-TOLERANT PATIENTS ONLY”** and **“DURAGESIC[®] should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC[®] 25 mcg/h.”**⁵⁵⁸ This same language was restated in the updated indications, and a contraindication was added stating that Duragesic is contraindicated “in patients who are not opioid-tolerant.”⁵⁵⁹

272. This change essentially extended the restriction in the indication for opioid-naïve patients from doses higher than 25 mcg to *all* doses, including the lowest dose. At the same time, a new 12 mcg/h titrating dose was introduced.⁵⁶⁰

⁵⁵⁴ JAN-MS-00907134 at 7-8.

⁵⁵⁵ JAN-MS-00907134 at 8.

⁵⁵⁶ Duragesic label, February 2005, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/19813s039lbl.pdf (last visited March 19, 2019) (emphasis added for significant changes).

⁵⁵⁷ Later changes to the indication, after generic Duragesic/fentanyl patches became available, are contained in Schedule 12.

⁵⁵⁸ JAN00222123 at 1 (emphases in original). The label defined patients who are considered opioid-tolerant as “those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.”

⁵⁵⁹ JAN00222123 at 2.

⁵⁶⁰ JAN00222123 at 2.

(b) Pre-Approval FDA Correspondence

273. The FDA Medical Officer Review (“MOR”) of the NDA for Duragesic was authored by Dr. Curtis Wright.⁵⁶¹ Even before reviewing the NDA for Duragesic, Dr. Wright raised concerns with Janssen about diversion of the product.⁵⁶² At a pre-approval meeting with Janssen in August 1989, he asked about “the potential for extraction of fentanyl from used or unused systems” and suggested “ways to reduce the abuse potential,” including incorporation of naloxone.⁵⁶³

274. At a subsequent pre-approval meeting with Janssen regarding abuse liability and diversion issues with Duragesic, Dr. Wright also advised Janssen that it would “need special precautions to keep this product on target for the cancer pain population.”⁵⁶⁴

275. In the Duragesic MOR, Dr. Wright noted, “It is the opinion of the reviewer that once the clinicians learn that the TTS [Transdermal Therapeutic System] fentanyl system can provide continuous opioid analgesia through the night, that the system will be used in a much broader clinical population than intended. This spread beyond the use which has been evaluated in clinical trials is common to many drugs and represents an unknown hazard for all of them. It is not unsafe, by itself, but the extent of such use should be estimated, the risks identified, and their management outlined.”⁵⁶⁵

276. Dr. Wright also stated in the MOR that “[i]n the opinion of the reviewer, the system is approvable, but will require Phase IV obligations to be placed on the sponsor to ensure

⁵⁶¹ As noted in the Purdue section above, Dr. Wright later authored the Medical Officer Review of the NDA for OxyContin and ultimately left FDA to work for Purdue Pharma.

⁵⁶² JAN-MS-02908031.

⁵⁶³ *Id.*

⁵⁶⁴ JAN-MS-02909945 at 3.

⁵⁶⁵ JAN-MS-00551711 at 316.

that the introduction of the system into clinical practice is not accompanied by extensive improper use and consequent morbidity and mortality. The available data shows that use of the TTS fentanyl system will result in an increased total opioid dose to the patient over PRN dosing, which is a major advantage in clinical situations where under-dosing is the norm. If TTS fentanyl use is extended to clinical situations where this is not the case, opiate over-dosage is likely to occur. As use of the system spreads beyond the post-operative period and the “healthy” cancer patient it will be given to patients who are receiving concomitant medications which affect respirations and serious adverse events due to drug-drug and drug-disease interactions will occur. It is not possible on the basis of the available data to predict the probable frequency or severity of these reactions, but the advertising and detailing of the system will be critical in preventing overdose attributable to its use.”⁵⁶⁶

277. I have been unable to locate in the record any evidence that Janssen conducted Phase IV studies into improper use and consequent morbidity and mortality.

278. Dr. Wright further stated in his “safety conclusions” section regarding clinical trials of Duragesic that trials in postoperative settings revealed the adverse event of respiratory depression at rates of 3% to 6%. Dr. Wright stated, “It may reasonably be expected that the frequency of this adverse effect will increase should TTS use spread into more debilitated populations on the medical services and into less well supervised postoperative settings.”⁵⁶⁷

279. The “Dissolution Review Portion” of FDA’s review of the Duragesic NDA appears to have stated that the studies of Duragesic “indicate that all of the TTS patches deliver more fentanyl than expected. From the data presented by the sponsor concerning residual fentanyl, it can be shown that, on the average, all of the subjects in the studies received 150% of

⁵⁶⁶ *Id.*

⁵⁶⁷ *Id.*

the target dose in 24 hours. This excessive release of fentanyl can have significant consequences (safety) given that the fentanyl has a narrow therapeutic range.”⁵⁶⁸

280. As demonstrated below, many of Dr. Wright’s predictions came true. Duragesic was used in a “much broader clinical population than intended,” due to Janssen’s improper marketing of the drug for broader indications, its understatement of the risks of the drug in its promotions, and its overstatement of its benefits. Because of this improper marketing, Duragesic use was in fact extended to clinical situations beyond where under-dosing is the norm, substantial numbers of overdoses did occur, and excessive release of Duragesic did have significant safety consequences. Spurred by Janssen’s marketing, use of Duragesic did spread beyond the post-operative period and the “healthy” cancer patient. While Dr. Wright considered advertising and detailing of Duragesic critical to preventing overdoses, that depends on it being careful and accurate; the misleading nature of the advertising and detailing Janssen actually employed in fact made overdoses and abuse more likely.

2. Janssen’s Marketing of Duragesic Broadened its Indications, Expanding the Use of Long Acting Opioids and Contributing to the Change in the Practice of Medicine.

(a) Janssen’s Marketing Focus Shifted from Cancer Pain to Non-Cancer Chronic Pain in the Mid-1990s.

281. The initial focus of Janssen’s marketing of Duragesic was on cancer patients. A “Positioning Evolution Overview” dated June 2002 provides a “Duragesic Ad Campaign Overview” timeline that tracks the evolution of the drug’s marketing. The first entry in the timeline, for March 1991, is “Focus on introduction of patch technology providing 72 hours of relief to malignant chronic pain patients.”⁵⁶⁹

⁵⁶⁸ JAN-MS-02908681 at 7-8. The stand-alone document could not be located in the documents produced by Janssen.

⁵⁶⁹ JAN-MS-00309606 at 7.

282. Starting in the mid-1990s, at around the same time that Purdue introduced OxyContin CR, Janssen's promotion of Duragesic shifted from a focus on cancer pain to chronic pain generally, and introduced comparisons to oral opioids. The "Duragesic Ad Campaign Overview" timeline noted that as of May 1994 there was a "Shift away from limiting consideration to only malignant patients" to "Promotion of around-the-clock control highlights benefits of 72 hour efficacy in limiting breakthrough pain associated with oral medications."⁵⁷⁰

283. A Duragesic "Journal Advertising Overview" shows that from April 1995 to July 1997, Janssen's "Core Campaign Journal Ad" for Duragesic used the headline "Why Interrupt These Moments With Oral Opioid Dosing?" and the tagline "Chronic Pain Control That Goes On."⁵⁷¹

284. A November 12, 1999 bulletin Janssen sent to its Sales Force reported on an article in the British Medical Journal regarding a physician who was disciplined for undertreating pain.⁵⁷² The bulletin noted, "One of the issues that is driving the rapid expansion of the pain market is the changing attitude towards the treatment of chronic, severe pain. While many physicians are becoming more comfortable with opioids and more aggressive treatment options, there are still situations where patients do not receive the treatment they need."⁵⁷³ The bulletin told the Sales Force that the case "underscores the importance of what you do on a daily basis...."⁵⁷⁴

⁵⁷⁰ *Id.*

⁵⁷¹ JAN-MS-00305469 at 5-7.

⁵⁷² JAN-MS-02728546.

⁵⁷³ *Id.*

⁵⁷⁴ *Id.*

285. A Duragesic Business Plan for 2001, dated 2000, stated that Duragesic's "vision" was to be the "first choice of chronic pain patients for around-the clock-therapy."⁵⁷⁵ The Plan noted that "Non-malignant market is the growth opportunity," but stated just below this point that "DURAGESIC data is non-existent."⁵⁷⁶ A SWOT analysis in the same document stated that "opioid acceptance for non-malignant pain" was an opportunity for Duragesic, but that "limited clinical data" was a weakness. Elsewhere in the same plan is the statement "need non-malignant pain data (lower back, OA [osteoarthritis]/RA [rheumatoid arthritis])."⁵⁷⁷

286. In May 2000, Janssen approached FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) about its plan to do Direct to Consumer (DTC) advertising for Duragesic. While Janssen ultimately decided after several meetings with FDA not to pursue the DTC advertising plan,⁵⁷⁸ the interactions between it and DDDMAC regarding the plan highlight the shifting focus in Duragesic's promotion from malignant pain treated by pain specialists to non-malignant pain.

287. DDMAC's initial response to Janssen's DTC advertising plan was that it "[wa]s not thrilled by the idea but there [we]re no regulations preventing us from moving forward."⁵⁷⁹ At Janssen's next meeting with FDA regarding the plan, DDMAC Branch Chief Dr. Nancy Ostrove "expressed a concern about the patient population being targeted" and noted her "recollection was that we would target cancer patients."⁵⁸⁰ Janssen's representative "clarified" that Janssen's "market research had identified back pain and arthritis pain suffers as undertreated and

⁵⁷⁵ JAN-MS-00618253 at 3.

⁵⁷⁶ *Id* at 19.

⁵⁷⁷ *Id* at 18.

⁵⁷⁸ JAN-MS-00480543.

⁵⁷⁹ JAN-MS-00479787 at 2.

⁵⁸⁰ JAN-MS-00479784 at 2.

potentially appropriate candidates for Duragesic.” DDMAC’s representative responded that “this was fine but the message needs to be clearer that the drug is for severe pain, not ‘your everyday back pain.’”⁵⁸¹

288. At the next meeting between Janssen and FDA, Dr. Ostrove raised FDA’s concern that “Duragesic is currently being used by physicians experienced with pain management, who are comfortable with using and prescribing Duragesic. DTC would likely increase use by primary care physicians who are inexperienced with the product. This leads to FDA’s concern of increased inappropriate use and increased adverse events.”⁵⁸² Dr. Ostrove also suggested Janssen advise patients in the DTC ads “that their doctor may not be the right person to prescribe Duragesic and they may need to be referred to a specialist. This is particularly important as it will likely be the opioid-naïve patients who are going to their primary care physician as a result of the ad.”⁵⁸³

289. In a June 2001 presentation to Janssen by Discovery NJ entitled “Growing Market Share in 2002--Medical Education Tactics in Support of Duragesic,” “Expand Duragesic use in non-malignant pain” is identified as a “Key Strategy” for which “Role/Importance of Education” is shown as “High.”⁵⁸⁴ “Supporting tactics” for this key strategy include a “National CME Initiative;” a “KOL Development and Management Plan;” a plan to target particular publications such as JAMA with articles on Duragesic, including suggestions of possible titles, authors, and key messages; and a speakers’ bureau.⁵⁸⁵

⁵⁸¹ *Id.*

⁵⁸² JAN-MS-00479781 at 2.

⁵⁸³ *Id.*

⁵⁸⁴ JAN-MS-00780131 at 3.

⁵⁸⁵ *Id.* at 4, 7.

290. A 2003 “Duragesic Public Relations Activities” PowerPoint identified “Expand in non-malignant pain categories (back pain)” as a “Core Duragesic Brand Strategy,” and “Target non-malignant severe chronic pain states (primarily lower back)” as a “2003 PR Objective.”⁵⁸⁶

290.1. Under “Direct-to-Patient Awareness,” the presentation advocated that Janssen “[u]se broad, unbranded messages and stories about serious chronic back pain to attract potential patients,” and “[d]raw potential patients to ‘opt-in’ to branded Duragesic information on Internet.”⁵⁸⁷

290.2. It further suggested creating a website called www.chronicbackpain.com to “utilize Internet to engage, capture chronic back pain patients.”⁵⁸⁸

290.3. The PR plan explained that the “primary emphasis on lower back pain” was because “[a]long with osteoarthritis” lower back pain was “identified as key growth opportunity,” but “[u]nlike OA, chronic back pain is not ‘owned’ by any medication or pharmaceutical company.”⁵⁸⁹

291. A September 2003 presentation for Janssen by marketing firm ZS Associates entitled “Duragesic® PhysPulse® Brand Monitoring and Performance Enhancement Study” identified “a significant opportunity for greater Duragesic usage for applications outside of cancer pain, especially back pain.”⁵⁹⁰

⁵⁸⁶ JAN-MS-00776219 at 4.

⁵⁸⁷ JAN-MS-00776219 at 17.

⁵⁸⁸ JAN-MS-00776219 at 9-15.

⁵⁸⁹ JAN-MS-00776219 at 8.

⁵⁹⁰ JAN-MS-00306124 at 6, 43.

291.1. The presentation further urged that “Moving back pain from an opportunity area to a core application is an important objective for the brand,” and “Similar opportunities may be present in fibromyalgia, arthritis and neuropathic pain.”⁵⁹¹

291.2. The presentation suggested that “A shift in targeting and detailing frequency from Oncologists to PCPs and Pain Specialists may be required to drive greater consideration of Duragesic for these applications.”⁵⁹²

(b) Janssen’s Marketing Misrepresented Duragesic’s Efficacy and Risks for Chronic Non-Cancer Pain.

292. Janssen sent its sales force bulletins and training materials alerting them to studies of Duragesic for chronic non-cancer pain, and used professional file cards and similar materials in marketing that touted these studies.⁵⁹³ These promotional materials highlighted and at times overstated the studies’ positive findings for chronic non-cancer pain, while at times providing explanations for negative findings that attributed them to alleged flaws in the study design or in treatment, or to pre-existing conditions in the subjects. FDA’s DDMAC sent Janssen warning letters relating to misrepresentations it made regarding these studies in its promotional materials.

293. Janssen sent a September 2001 memorandum to its Field Sales Force regarding a study by Milligan et al. published in the *Journal of Pain* entitled “Evaluation of Long-term Efficacy and Safety of Transdermal Fentanyl in the Treatment of Chronic Noncancer Pain,”⁵⁹⁴

⁵⁹¹ JAN-MS-00306124 at 37, 43.

⁵⁹² JAN-MS-00306124 at 43.

⁵⁹³ JAN-MS-02728460 (bulletin re Simpson study); JAN-MS-00776447 (Duragesic self-study guide for sales representatives); JAN-MS-00776565 (bulletin re Milligan study); JAN-MS-00299212 (file card); JAN-MS-02757939 (file card); JAN-MS-02757751 (sales aid for sales representatives); JAN-MS-02757589 (sales aid for sales representatives).

⁵⁹⁴ JAN-MS-00311759.

and an editorial in response by Perry Fine.⁵⁹⁵ Janssen advised the Sales Force that the study's authors stated that Duragesic provided "stable, sustained, long-term pain control,"⁵⁹⁶ although the study had found that 1/3 of its subjects did not respond to Duragesic. Janssen explained this fact by stating that it "coincided with Perry Fine's comments (see editorial) that a process of trial and error is often needed to achieve adequate pain management."⁵⁹⁷ With regards to the study's reported global efficacy rate of 42%, Janssen advised its Sales Force that "[a] possible explanation for the low rate of global efficacy is that... the results for the global efficacy measurement did not include a "moderate" rating,"⁵⁹⁸ an explanation not offered by the study itself.

294. As to the study's reported withdrawal (drop-out) rate of 43%, Janssen's advised its Sales Force that the study's authors found "the incidence of AEs [adverse events] and the rate of withdrawal from the trial are relatively high but neither unusual nor unexpected considering the baseline clinical status of the study population."⁵⁹⁹ The Bulletin further advised the Sales Force that the fact that withdrawals due to adverse events or insufficient response diminished after 6 months "may indicate that most of the withdrawals [were] secondary to insufficient response or AEs may be related to improper titration and lack of tolerability to the transient side effects of TDF [transdermal fentanyl, i.e., Duragesic],"⁶⁰⁰ again an explanation not found in the study.

⁵⁹⁵ PPLPC020000014935 (Fine P.G., Opioid selection: plaudits, pitfalls, and possibilities. *Journal of Pain*. 2(4) August, 2001: 195-6.)

⁵⁹⁶ JAN-MS-00776565 at 3.

⁵⁹⁷ See JAN-MS-00776565.

⁵⁹⁸ *Id.*

⁵⁹⁹ *Id.*

⁶⁰⁰ *Id.*

295. Canadian health authorities had previously commented to Janssen that the studies it submitted in support of the use of Duragesic for chronic pain, including the Milligan study, involved only patients who were already taking potent opioids before entering the studies.⁶⁰¹ The Canadian authorities further noted that “the treatment of opioid naive patients with transdermal fentanyl for postoperative pain has resulted in deaths due to respiratory depression in the past.”⁶⁰² In its reply to the Canadian comments, Janssen stated “We acknowledge that the experience in opioid naive non-cancer patients is limited.”⁶⁰³ No such acknowledgement was made in Janssen’s Bulletin to its Sales Force about the Milligan study.

296. Janssen also did not advise its Sales Force in the Bulletin that the stability of pain control achieved in the study came at the cost of a near doubling of the mean dose of Duragesic over 12 months, even with unlimited access to rescue dosing.⁶⁰⁴ The Bulletin further did not disclose that the Milligan study had reported 3 cases of drug abuse/dependence (a rate of 1%), and 11 cases of opioid withdrawal syndrome (a rate of 3%)⁶⁰⁵ or that Janssen scientists had previously concluded based on analysis of data from the study that the “probability of tolerance with long term Duragesic use was low but not negligible,” with the global tolerance probability stated as 22%, and higher in those whose underlying disease deteriorated (28%) or improved (32%).⁶⁰⁶ This prior tolerance analysis, dated February 2001, found based on the Milligan study’s data that tolerance developed between 1 and 3 months of Duragesic use, and therefore

⁶⁰¹ JAN-MS-00901369 at 12.

⁶⁰² *Id.*

⁶⁰³ *Id.*

⁶⁰⁴ JAN-MS-00311759 at 6.

⁶⁰⁵ JAN-MS-00311759 at 5-6.

⁶⁰⁶ JAN-MS-00901949 at 4-5.

recommended that a guideline for long term treatment monitoring be introduced, with dose increases triggering reevaluation of the underlying disease.⁶⁰⁷

297. The Janssen scientist who co-authored the tolerance analysis above, Birgitte Kuperwasser, Associate Director of Global Analgesia R&D, later sent an email to other Janssen employees in which she noted that the Milligan study (referred to in her email as FEN-INT-13) was an “open single arm study to evaluate long term safety,” and stated that she wanted to “reiterate” concerns that had been raised previously regarding using the Milligan study (as well as two other post-marketing studies) “to make an argument for efficacy.”⁶⁰⁸ In (re)raising these concerns, Dr. Kuperwasser noted that “[t]hese studies have not [sic] the appropriate design neither the end points to make a case for efficacy.”⁶⁰⁹ Janssen did not disclose in its Bulletin to its Sales Force that its scientist who had analyzed the Milligan study had concerns about using its findings to show Duragesic’s efficacy.⁶¹⁰

298. Janssen also did not disclose in the Bulletin that the Milligan study was supported by a grant from the Janssen Research Foundation, and the lead author had received financial support from Janssen.⁶¹¹

299. In sum, in my opinion, in communicating to its Sales Force about the Milligan study regarding the use of Duragesic for chronic non-cancer pain, Janssen overstated the study’s findings on efficacy and sought to explain away negative results in the study as due to pre-

⁶⁰⁷ *Id.* at 8, 11.

⁶⁰⁸ JAN-MS-00901946.

⁶⁰⁹ *Id.*

⁶¹⁰ When Janssen proposed using the Milligan study again in Duragesic promotional materials in 2007, Vince Brett, Janssen Associate Director of Medical Communications, recommended deleting it because it was “loaded with inconsistencies, errors, and omissions of data, which calls into question the integrity of the results.” JAN-MS-00747497 at 1, 4.

⁶¹¹ JAN-MS-00311759 at 759.

existing patient characteristics, alleged improper treatment by physicians, or the fact that the study design did not include certain categories, rather than issues with Janssen's drug. These explanations were suggested by Janssen to its Sales Force even when not offered by the study's authors. Janssen also did not inform its Sales Force of the substantial increase in dosing over the study, the adverse events in the study relating to abuse/dependence and its scientists' findings and recommendations regarding them, its scientist's concerns about using the study to show efficacy, or its sponsorship of the study.

300. In a January 21, 1998 memorandum to its Field Sales Force regarding an open label study by Richard Simpson et al. published in 1997 in the *Journal of Pain and Symptom Management* entitled "Transdermal Fentanyl as Treatment for Chronic Low Back Pain,"⁶¹² Janssen advised its Sales Force that the study results suggested "that patients on DURAGESIC treated for chronic low back pain report greater improvement in pain relief and disability than those who received oral opioids," and that "use of Duragesic may be associated with less disability caused by chronic lower back pain."⁶¹³ In professional file cards and other materials used by sales representatives, Janssen likewise cited the Simpson study for its claim that Duragesic "[de]monstrated effectiveness in chronic back pain with additional patient benefits," and also claimed that "[a]ll patients who experienced overall benefit from DURAGESIC would recommend it to others with chronic low back pain."⁶¹⁴

301. In a September 2004 warning letter to Janssen regarding this file card, FDA's DDMAC found that the Simpson study was "inadequate to support th[ese] claim[s], because it

⁶¹² JAN-MS-00591572.

⁶¹³ JAN-MS-02728460 at 2. Janssen likewise did not disclose in this Sales Force memorandum that it funded the Simpson study. JAN-MS-00591572 at 572.

⁶¹⁴ JAN-MS-00299212; JAN-MS-02757939; JAN-MS-02757589.

was an open-label, single-arm trial with no control group,” and further stated “[w]e are not aware of substantial evidence or substantial clinical experience to support th[ese] claim[s].”⁶¹⁵ DDMAC found these claims to be “unsubstantiated effectiveness claims,” that they and other misleading claims on the file card were “serious” violations and constituted misbranding, and requested that Janssen “immediately cease dissemination” of the promotional file card and come up with a plan for corrective action.^{616 617}

302. In a 2002 Janssen Sales Representative Self-Study Guide, one objective of a Duragesic module was to “Explicate the Simpson study and articulate the key selling points.”⁶¹⁸ The same Guide featured another Duragesic module in which the sales representative was to describe “the causes of chronic back pain,” as well as “the etiology of degenerative joint disease” and “types of HIV/AIDS-related pain.”⁶¹⁹

303. In 1998 and 2000, FDA’s DDMAC issued additional warning letters to Janssen for promotion of Duragesic for unapproved uses.

304. On March 5, 1998, DDMAC issued a warning letter to Janssen regarding promotional posters for Duragesic that contained bold type at the top claiming that Duragesic is “recommended for use in chronic pain.”⁶²⁰ DDMAC noted, however, that the full approved indication stated that Duragesic is indicated for chronic pain “in patients who require continuous opioid analgesia for pain *that cannot be managed by lesser means*” (emphasis added), language

⁶¹⁵ JAN-MS-00779345.

⁶¹⁶ *Id.*

⁶¹⁷ Janssen responded that it disagreed with DDMAC’s position but would discontinue the file card and promotional materials with the same or similar representations. JAN-MS-00238384. Janssen also agreed to send a “Dear Doctor Letter” to physicians advising them of FDA’s warning letter. *See* JAN-MS-00191340.

⁶¹⁸ JAN-MS-00776447 at 9; JAN-MS-00776446.

⁶¹⁹ JAN-MS-00776447 at 6.

⁶²⁰ JAN-MS-00238335 at 2.

which was not included in the bold type at the top of the poster.⁶²¹ The agency found that “the presentation of the full indication near the bottom of the poster in small, inconspicuous type size” was “misleading and overwhelmed by the more prominent claim of chronic pain at the top of the poster,” and therefore determined that Janssen was promoting Duragesic “for a much broader use than that recommended in the approved product labeling.”⁶²²

305. On March 30, 2000, DDMAC issued a warning letter to Janssen regarding homemade promotional pieces for Duragesic sent to thousands of doctors which stated “It’s not just for end stage cancer anymore!”⁶²³ DDMAC found that this claim “suggests that Duragesic can be used for any kind of pain”—rather than for chronic pain in patients requiring continuous opioid treatment for pain that cannot be managed for lesser means—and thus promoted Duragesic “for a much broader use” than in the label and was misleading.⁶²⁴

306. The call notes of Janssen’s sales representatives show that into 2004 they were frequently promoting Duragesic to prescribers for lower back pain and arthritis,⁶²⁵ consistent with the marketing materials and Sales Bulletins above. Some of these call notes indicate that the sales representatives were also citing to the Milligan and Simpson studies referenced in the sales bulletins noted above in promoting Duragesic for lower back pain.⁶²⁶ For example, one Ohio call

⁶²¹ *Id.*

⁶²² *Id.*

⁶²³ JAN-MS-00238338 at 2, 7.

⁶²⁴ *Id.*

⁶²⁵ JAN-OH-00000004; JAN-OH-00000005; JAN00118956 (11 calls in 1998, 4 calls in 1999, 1 call in 2003, and 11 calls in 2004). *See also* Schedule 11.

⁶²⁶ JAN-OH-00000005.

note from April 2003 states “presented simpson study. She said they have a lot of back pain pts on short-actings atc. Asked her to recommend Duragesic to those pts.. she said yes.”⁶²⁷

307. In my opinion, Janssen’s marketing of Duragesic broadened its indications beyond the label, and thereby expanded the use of long acting opioids and contributed to the change in the practice of medicine.

3. Janssen’s Promotion of Duragesic Understated its Risk and Overstated its Benefits.

(a) Janssen Promoted Duragesic as Superior to Oral Opioids, Especially OxyContin, Without Substantial Evidence.

308. After Purdue’s OxyContin entered the market, Janssen began to promote purported advantages of the Duragesic patch over oral opioids with regards to convenience and improved functioning.

309. From late 1995 through mid-1998, Janssen’s marketing materials used the tagline “Stops the Pain Not the Patient.”⁶²⁸ Its advertisements used headlines such as “Why interrupt these moments with oral opioid dosing?” and “Between the constant pill taking and the side effects, I got exhausted just trying to control my pain,” and featured patients talking about the constipation suffered by those on “pain pills.”⁶²⁹

310. From late 1998 to late 2000, Janssen’s key tagline was “Round the Clock Living” and its advertisements used headlines such as “With pain pills, it was like punching a clock every four hours.”⁶³⁰

⁶²⁷ *Id.*

⁶²⁸ JAN-MS-00305469.

⁶²⁹ *Id.* at 5-8.

⁶³⁰ *Id.* at 5-8.

311. Starting in late 2000, Janssen's marketing tagline became "Life, Uninterrupted," with promotional materials featuring friends, couples and families being active together.⁶³¹ These materials promoted Duragesic on the basis that it offered "72 hours of uninterrupted pain relief"⁶³² and fewer peaks and troughs than oral opioids,⁶³³ and "relieve[d] the burden of taking pills 2 or more times a day."⁶³⁴ The promotions included patient quotes such as "Pain relief lasted longer with Duragesic than with the pills I was taking,"⁶³⁵ and "The patch took away the pain and let me take fewer pills."⁶³⁶

312. By this time, Janssen had begun closely tracking Purdue's sales and marketing of OxyContin. In a January 17, 2000 email, Chis Johnson, of Janssen's Sales Training Department, advised other Janssen employees, "In order for us to reach our Duragesic goals for the year 2000, we need to know as much about the competition as possible. We now have the capabilities of doing this with the Oxycontin Backgrounder. Please take the time to read through this material in its entirety..."⁶³⁷ The OxyContin Backgrounder was also distributed as part of the 2002 Janssen Sales Representative Self-Study Guide, which taught sales representatives how to "Differentiate between Duragesic and OxyContin."⁶³⁸

313. At the same time Janssen was utilizing the marketing messages above claiming Duragesic's superiority over "pain pills," Janssen explored a partnership with Purdue to co-

⁶³¹ JAN-MS-00305469 at 15.

⁶³² JAN-MS-02757939 at 2; JAN-MS-02757589 at 2; JAN-MS-02757751 at 2; JAN-MS-02757583 at 2.

⁶³³ See JAN-MS-02757939 at 2; JAN-MS-02757589 at 2; JAN00118955; JAN-OH-00000004; JAN-OH-00000005; JAN00118956; JAN-MS-02757751 at 2; JAN-MS-02757583.

⁶³⁴ JAN-MS-02757939 at 3.

⁶³⁵ *Id.*

⁶³⁶ *Id.* at 4.

⁶³⁷ JAN-MS-02727829

⁶³⁸ JAN-MS-00776447 at 8-9.

promote Duragesic and OxyContin, designated “Project Pearl.” The project looked at whether the drugs could “be positioned to physicians in a complementary way”⁶³⁹ and proposed “mirror[ing] Purdue and Janssen sales force[s].”⁶⁴⁰

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316. Although Project Pearl was apparently ultimately abandoned, Janssen continued to track OxyContin’s sales and marketing, with its focus shifting to taking market share from OxyContin. A February 2002 Duragesic Sales Force Presentation stated “Must take share from

⁶³⁹ JAN-MS-00456650.

⁶⁴⁰ JAN-MS-01051754 at 35.

⁶⁴¹ JAN-MS-02727829

⁶⁴² JAN-MS-00776447 at 8-9.

⁶⁴³ JAN-MS-00456650.

⁶⁴⁴ JAN-MS-01051754 at 35.

OxyContin” and contained multiple graphs comparing sales of the two drugs.⁶⁴⁵ The presentation noted that “despite media focus, OxyContin loses only 2.5 share points” and “Duragesic share growth has slowed, must be aggressive to meet 2002 goals.”⁶⁴⁶ It further compared sales of the two drugs among physicians in different sales deciles, revealing that while OxyContin had a larger market share than Duragesic in all deciles, the gap was largest in the highest decile prescribers. The slide with the data stated “Need to drive share in higher deciles” at top, and another slide stated “Utilize all available resources with high decile physicians.”⁶⁴⁷

317. Similarly, a May 2002 Sales Force District Meeting Presentation had a slide entitled “Beat OxyContin” with the bullet points “Sell Duragesic on every call” and “Take share from OxyContin.”⁶⁴⁸ A June 2002 Analysis of Duragesic Brand Prescribing tracked OxyContin prescribers by specialty and noted that “As the number of writers of Oxycontin has declined significantly in this Other Specialty group, it seems like Duragesic is gaining at the expense of OxyContin.”⁶⁴⁹

318. Janssen was also tracking Purdue’s sales force for OxyContin. A December 2002 email from Jay Stahl of Janssen’s Business Intelligence unit, responding to an inquiry from Chris Matteson, Associate Director of Sales Operations, provided details regarding the number of OxyContin sales representatives at different points in time and stated “Hope this helps with the

⁶⁴⁵ JAN-MS-00785983.

⁶⁴⁶ *Id.* at 8.

⁶⁴⁷ *Id.* at 12, 15.

⁶⁴⁸ JAN-MS-00246939 at 3.

⁶⁴⁹ JAN-MS-00787243 at 18.

Duragesic business plan.”⁶⁵⁰ A 2002 slide presentation compared the deployment of sales representatives and sales calls for OxyContin and Duragesic.⁶⁵¹

319. A 2003 Duragesic “Positioning/Message/Campaign--Evolution Overview” presentation provided to Janssen by KPR shows that in 2001 and 2002 KPR conducted field testing of different promotional messages for Duragesic through several surveys and other tools that compared Duragesic to OxyContin.⁶⁵² The field testing included use of the Simpson and Milligan studies mentioned above.⁶⁵³

320. The September 2003 Duragesic Brand Monitoring and Performance Enhancement Study presentation by ZS Associates contained graphs of IMS sales data showing that “Duragesic continues to gain share from OxyContin.”⁶⁵⁴ The presentation also cited results from physician surveys showing that “Duragesic is perceived to perform better than OxyContin on most attributes of high stated importance,” including “able to regain functionality.”⁶⁵⁵ The functionality message was utilized in subsequent promotional materials such as a December 2003 visual aid for pharmacists, which highlighted the claim that Duragesic provided “Chronic pain relief that supports functionality” and “improvements in physical social functioning.”⁶⁵⁶

⁶⁵⁰ JAN-MS-02990169.

⁶⁵¹ JAN-MS-00780336 at 3.

⁶⁵² JAN-MS-00306327 at 8, 9, 20, 21, 25.

⁶⁵³ JAN-MS-00306327 at 17, 19.

⁶⁵⁴ JAN-MS-00306124 at 8.

⁶⁵⁵ JAN-MS-00306124 at 8, 16.

⁶⁵⁶ JAN-MS-02757583 at 6.

(b) DDMAC Warned Janssen That its Functionality Claims and Superiority Claims Comparing Duragesic to Oral Opioids Were Misleading.

321. DDMAC issued warning letters to Janssen for various marketing materials that made superiority claims and promoted improved functioning like those above, which FDA considered to be false and misleading. In March 1998, DDMAC warned Janssen that a claim it made on a convention poster that Duragesic caused significantly less constipation than morphine was not supported by substantial evidence.⁶⁵⁷ The poster featured a statement that “[t]he constipation got so bad, I was afraid to swallow my pain pills,” accompanied by a chart comparing the incidence of constipation with Duragesic versus sustained release morphine reported in an open label study.⁶⁵⁸ FDA noted that claims of superiority to competitor drugs require substantial evidence, generally in the form of two adequate and well-controlled, head-to-head studies of the drugs. FDA did not consider the study cited to meet this standard.⁶⁵⁹

322. In fact, DDMAC found that Janssen had “selectively present[ed] the results” of the study to “provide the misleading impression that the tolerability profile of [Duragesic] is superior to sustained-release morphine.”⁶⁶⁰ DDMAC noted that Janssen “fail[ed] to present data” from the study showing that 1) subjects on Duragesic reported more sleep disturbances and shorter sleep than those on sustained release oral morphine; 2) the incidence of abdominal pain, dyspnea and sweating were “markedly higher” with Duragesic; and 3) more Duragesic subjects than morphine subjects required rescue medication.⁶⁶¹

⁶⁵⁷JAN-MS-00238335.

⁶⁵⁸*Id.*

⁶⁵⁹*Id.*

⁶⁶⁰*Id.* at 2.

⁶⁶¹*Id.*

323. In the same letter, DDMAC found similar faults with another Janssen promotional poster in which Janssen combined the statement “I needed the relief the pain pills gave me, but the constipation kept me from doing the things I wanted to do ... “ with the claim that “Duragesic provides less frequency and impact of side effects.”⁶⁶² DDMAC found that the combination of these statements “impl[ied] that Duragesic is superior to sustained-release oral morphine” without substantial supporting evidence.⁶⁶³

324. In addition, in its 1998 letter DDMAC warned Janssen that the tagline “Stops the Pain Not the Patient” was false and misleading because it implied that Duragesic was “not associated with impairment of mental or physical abilities,” even though the label contained a precaution that the use of strong opioid analgesics impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving.⁶⁶⁴

325. DDMAC concluded its 1998 letter by ordering Janssen to “immediately suspend all promotional activities and materials that convey or contain the allegedly violative claims or information identified in this letter until these allegations are resolved.”⁶⁶⁵

326. In its March 20, 2000 warning letter, DDMAC warned Janssen regarding several “homemade” promotional pieces that contained some of the same misrepresentations noted in the 1998 warning letter.⁶⁶⁶ Specifically, FDA found the claim in these materials of “Significantly LESS constipation!” to be false or misleading because it “minimize[d] the risk of constipation that is associated with Duragesic therapy” and suggested that “Duragesic is associated with

⁶⁶² *Id.*

⁶⁶³ *Id.*

⁶⁶⁴ *Id.* at 2-3.

⁶⁶⁵ *Id.* at 3.

⁶⁶⁶ JAN-MS-00238338 at 2.

significantly less constipation than other available opioids” without substantial evidence.

DDMAC referred Janssen back to its 1998 warning letter addressing the same issue.⁶⁶⁷ The March 2000 warning letter made the same findings regarding Janssen’s claim in the homemade pieces that “Duragesic results in much less Constipation compared to Oxycontin (Senokot \$1.00/day).”⁶⁶⁸

327. DDMAC also warned Janssen in its March 2000 warning letter that Janssen’s claim of “Preferred regimen: 2 x per week versus 2 x per day!” suggested that patients “prefer Duragesic to other available oral opioids that are taken twice daily” without substantial evidence, and was therefore false or misleading.⁶⁶⁹

328. Janssen was also taken to task in DDMAC’s March 2000 letter for its unsubstantiated and misleading quality of life claims that “And the #1 reason to convert your patients to the Duragesic patch: QUALITY OF LIFE,” and “...without pain, patient’s sleep better, increase daily activities, and spend more quality time with their families.”⁶⁷⁰ DDMAC noted that such “health related quality of life claims...require substantial supporting evidence in the form of adequate and well controlled studies designed to specifically assess these outcomes.”⁶⁷¹

329. Janssen continued to promote Duragesic utilizing very similar misleading claims to those above even after the 1998 and 2000 DDMAC warning letters.

⁶⁶⁷ *Id.*

⁶⁶⁸ JAN-MS-00238338 at 5.

⁶⁶⁹ JAN-MS-00238338 at 4.

⁶⁷⁰ *Id.*

⁶⁷¹ *Id.*

329.1. A March 2001 professional file card claimed that Duragesic “relieve[d] the burden of taking pills 2 or more times a day.”⁶⁷²

329.2. The same file card and a March 2002 sales aid both claimed Duragesic “significantly reduced nighttime awakenings,” citing the Simpson study.⁶⁷³

329.3. The March 2002 sales aid also claimed Duragesic provided “significant improvement in disability,” also citing Simpson, and “improvements in physical social functioning.”⁶⁷⁴

329.4. The December 2003 visual aid for pharmacists similarly claimed that Duragesic provided “Chronic pain relief that supports functionality” and “improvements in physical social functioning.”⁶⁷⁵

330. In December 2000, Janssen met with FDA to discuss a trial it planned to do to support a superiority claim that Duragesic exhibited greater patient satisfaction than OxyContin.⁶⁷⁶ Instead of an “adequate and well controlled study” of the type DDMAC had advised Janssen in its 1998 letter would be needed for such a superiority claim,⁶⁷⁷ however, Janssen proposed an open-label study, which FDA quickly rejected as inadequate to support any comparative efficacy claim.⁶⁷⁸

331. In the 2004 DDMAC warning letter discussed above in which DDMAC found that Janssen had misleadingly used the Simpson study to promote Duragesic as effective for

⁶⁷² JAN-MS-02757939 at 3.

⁶⁷³ JAN-MS-02757939 at 3; JAN-MS-02757589 at 3.

⁶⁷⁴ JAN-MS-02757939 at 3; JAN-MS-02757589 at 3.

⁶⁷⁵ JAN-MS-02757583 at 6.

⁶⁷⁶ JAN-MS-00654881.

⁶⁷⁷ JAN-MS-00238335.

⁶⁷⁸ JAN-MS-00654881.

lower back pain in a professional file card, DDMAC also warned Janssen regarding several other misleading claims similar to ones DDMAC had warned about in the prior letters above. DDMAC found that the file card made misleading claims of reduced nighttime awakenings and improvement in disability scores based upon the same study.⁶⁷⁹ DDMAC stated that “this uncontrolled study is inadequate to support such claims.”⁶⁸⁰

332. DDMAC’s 2004 warning letter also found that the file card made similarly unsubstantiated claims of improved physical and social functioning based on the Milligan study discussed above and another study.⁶⁸¹ DDMAC likewise found that these open-label studies did not support such claims.

333. Janssen’s taglines on the file card of “Work, uninterrupted,” “Life, uninterrupted” and “1,360 loaves and counting” (showing a baker at work) were found also found to be misleading by DDMAC because they implied improved social or physical functioning or improved work productivity without citing any support for these outcome claims.⁶⁸²

334. As noted above, DDMAC concluded in its 2004 warning letter by requesting that Janssen “immediately cease the dissemination of promotional materials for Duragesic the same as or similar to those described above... Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials.”⁶⁸³

⁶⁷⁹ JAN-MS-00779345 at 3-4.

⁶⁸⁰ *Id.* at 4.

⁶⁸¹ *Id.*

⁶⁸² *Id.* at 4.

⁶⁸³ *Id.* at 4.

335. While Janssen apparently did discontinue some of its promotions materials with similar messages to those DDMAC criticized in its 2004 letter,⁶⁸⁴ promotional materials with such messages had been in use by Janssen for several years, and had continued to be used even after prior DDMAC letters warned that some of the messages were misleading. Indeed, “Life, Interrupted” was Janssen’s main marketing tagline for Duragesic starting in 2000⁶⁸⁵ and was used in a number of promotional materials, including those described above.

336. Janssen also sought to keep using of the same misleading messages it had been warned about in DDMAC’s letters after 2004. In May 2005, DDMAC responded to Janssen’s request for advisory comments on a proposed Duragesic detail aid.⁶⁸⁶ DDMAC noted that the detail ad “present[ed] the claims ‘... chronic pain relief’ and ‘... chronic pain treatment...’ multiple times.”⁶⁸⁷ DDMAC found that these claims were “misleading because they imply that Duragesic is indicated for all types of chronic pain, which is inconsistent with the PI,” since the PI stated that Duragesic was indicated only for “persistent, moderate to severe pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means...”⁶⁸⁸ DDMAC referred Janssen back to the communications regarding DDMAC’s March 1998 warning letter about the same issue.⁶⁸⁹

337. Call notes made by Janssen sales representatives show they frequently promoted Duragesic based on the same messages of improved quality of life and functioning, and less

⁶⁸⁴ JAN-MS-00779353.

⁶⁸⁵ JAN-MS-00305469 at 15.

⁶⁸⁶ JAN-MS-00291349.

⁶⁸⁷ *Id.* at 2.

⁶⁸⁸ *Id.* at 2.

⁶⁸⁹ *Id.* at 2.

constipation, featured in the Janssen marketing materials found to be misleading by DDMAC.⁶⁹⁰

In doing so they often invoked the same studies DDMAC found inadequate to support such claims. For example, multiple call notes from 2004 stated “discussed increased functionality with duragesic - discussed [M]illigan study results,” while another 2004 note stated “[s]howed [doctor] the Milligan study and talked about physical and social functioning with concrete examples -- left him reprint -- he seemed impressed by the data.”⁶⁹¹ An Ohio sales note from 2004 stated “[w]ent over [S]impson study, and she agreed the QOL [quality of life] would be improved with increased sleep,”⁶⁹² while one from Illinois stated “Simpson and 72 hour continuous analgeia [sic] equals improved functioning.”⁶⁹³

338. A number of the Duragesic call notes also show that Janssen made superiority claims for its drug compared to OxyContin on quality of life/functioning and side effects. Ohio call notes from 1998 stated “gave him [doctor] reasons to use dur over ms/oxy. hit on nursing home advatages. quality of life, low side effects” and “also hit m/c advantages of using pro. dur aver oxy/mscotin. quality of life.”⁶⁹⁴ Others from Ohio and elsewhere claimed Duragesic caused less constipation than OxyContin-- “dur inst of oxy less const no paek [sic] and valley”⁶⁹⁵—and allowed for better sleep.⁶⁹⁶

339. Janssen’s Business and Public Relations plans for Duragesic also show the company sought to promote the drug as improving functionality. KPR’s 2003 Duragesic

⁶⁹⁰ JAN-OH-00000004; JAN00118955; JAN00118956 (17 calls in 1998, 3 calls in 1999, and 20 calls in 2004). *See also* Schedule 12.

⁶⁹¹ JAN00118956 (see notes dated February 10, 2004 and April 16, 2004).

⁶⁹² JAN-OH-00000005 (March 19, 2004 call note).

⁶⁹³ JAN00118955 (February 16, 2004 call note).

⁶⁹⁴ JAN-OH-00000004 (September 18, 1998 call note).

⁶⁹⁵ *Id.* (November 18, 1998 call note). *See also* JAN00118956 (March 24, 2004 call note).

⁶⁹⁶ JAN00118956 (March 5, 2004 call note).

“Positioning/Message/Campaign--Evolution Overview” presentation for Janssen asserted that field testing of promotional messages for Duragesic showed that “restoration of functionality represented ‘unused airspace’ and could be adopted as an advantageous point of differentiation,” and that “restoration of functionality is a key driver and can be owned.”⁶⁹⁷

340. The 2003 Public Relations Activities PowerPoint for Duragesic referenced above identified “[l]everage functionality” as a “core brand strategy” that dovetailed with a “focus on chronic lower back pain.”⁶⁹⁸ The Public Relations presentation asserted that “[f]unctionality” is a new way for patients to understand and discuss chronic pain and treatment effectiveness with their doctors,” and suggested having functionality on unbranded websites on chronic back pain, which would also discuss Duragesic as a treatment option.⁶⁹⁹ The presentation also recommended that Janssen “enlist 3rd party groups to drive messages about functionality as the new pain measurement paradigm,” and “target pain groups” such as the American Pain Foundation, American Chronic Pain Association, and National Pain Foundation.⁷⁰⁰

341. In my opinion, Janssen misleadingly promoted Duragesic as superior to oral opioids, especially OxyContin, without substantial evidence, and overstated its functionality benefits.

⁶⁹⁷ JAN-MS-00306327 at 2, 10.

⁶⁹⁸ JAN-MS-00776219 at 3.

⁶⁹⁹ *Id.* at 18.

⁷⁰⁰ *Id.* at 24.

4. Janssen Promoted Duragesic as Having No or Lower Abuse Potential, Particularly Compared with OxyContin, Without Substantial Evidence.

342. Janssen's sales call notes show that as early as 1998, it was promoting Duragesic as having "no abuse potential" or low risk of abuse, both in absolute terms and as compared to other opioids, especially OxyContin.⁷⁰¹

343. As early as 2000, Janssen saw the abuse issue with OxyContin as creating opportunities to distinguish Duragesic and increase its market share.⁷⁰² As early as 2001, Janssen acknowledged that "abuse potential of opioids will continue to be an issue—long-term impact on market growth uncertain."⁷⁰³ Janssen was aware of increasing OxyContin abuse.⁷⁰⁴

344. Janssen business plans for 2001 through 2004 identify limited or low abuse as a Duragesic strength and potential point of differentiation, note that the impact of OxyContin abuse on Duragesic may be favorable barring class restrictions, and note that a primary driver of increased Duragesic prescribing is abuse concerns with oral opioids.⁷⁰⁵

345. Yet Janssen's marketing materials for Duragesic, like Purdue's for OxyContin, claimed that addiction to opioids was rare, and downplayed the significance of dependence. A 2001 patient booklet claimed that "addiction is relatively rare when patients take opioids appropriately," and "physical dependence is not the same as addiction and is easily managed by gradually reducing dose of the drug."⁷⁰⁶

⁷⁰¹ JAN-OH-00000004.

⁷⁰² JAN-MS-00306718.

⁷⁰³ JAN-MS-00306718 at 28.

⁷⁰⁴ JAN-MS-00246850.

⁷⁰⁵ See JAN-MS-00785798, JAN-MS-00306718, JAN-MS-00780354, and JAN-MS-00723375.

⁷⁰⁶ JAN-MS-02757826 at 22.

346. Janssen sales aids in 2002 and 2003 cited DAWN data to claim fentanyl only accounted for less than 1% of emergency visits, stating that “physicians should not let concerns of physical dependence deter them from using adequate amounts of opioids in the management of severe pain when such use is indicated.”⁷⁰⁷ By this time, however, other documents show Janssen acknowledging that the low rate of mentions in DAWN may have been due to the data only capturing emergency room admissions.⁷⁰⁸

347. In 2003, KPR conducted market research for Janssen “to assess the potential value of a DURAGESIC abuse message resulting in share increase” in light of “the attention in the popular and professional media surrounding the abuse of long-acting opioids, most prominently OxyContin.”⁷⁰⁹

347.1. The research revealed that “this is an important factor but not a key driver in the decision to prescribe a LAO [long acting opioid],” and advised that “High-volume abuse messaging will have no impact on sales of DURAGESIC and would, in fact, cast a negative shadow on the brand.”⁷¹⁰

347.2. The KPR presentation did note that “DAWN data [was] extremely well received” in certain field studies regarding Duragesic messaging,⁷¹¹ and that “Research indicates that abuse potential is important, but it should be addressed ‘separately’ from core promotional campaign.”⁷¹²

⁷⁰⁷ JAN-MS-02757589 at 7; JAN-MS-02757583 at 588.

⁷⁰⁸ JAN-MS-02757589 at 7.

⁷⁰⁹ JAN-MS-00306327 at 2.

⁷¹⁰ JAN-MS-00306327 at 2, 8.

⁷¹¹ JAN-MS-00306327 at 19.

⁷¹² JAN-MS-00306327 at 9.

348. The September 2003 Duragesic Brand Monitoring and Performance Enhancement Study presentation by ZS Associates found that “abuse potential is the main reason for decreasing OxyContin” and concomitantly that “lower abuse potential and fewer peaks and troughs are the most commonly cited reasons for increasing prescribing of Duragesic.”⁷¹³ The presentation concluded that while “lower abuse potential is the leading reason for increased Duragesic use” and “efforts to foster awareness of abuse issues may help accelerate and maintain the shift to Duragesic,” such efforts “must be carefully designed to minimize negative effects on the class as a whole.”⁷¹⁴

349. Over the same time period, Janssen was receiving a substantial number of abuse or addiction related adverse event reports for Duragesic. For each of the three consecutive years from April 2000 until April 2003, between 134 and 155 such reports were reported by Janssen in its Periodic Safety Update Reports, with those annual totals including between 20 and 55 cases where the abuse resulted in death.⁷¹⁵

350. The tension between, on the one hand, Janssen’s internal acknowledgement of abuse of Duragesic and the lack of data to support its lower abuse claims, and on the other, its continued promotion of the drug as less abuse prone than OxyContin, showed in a February 2000 discussion of Janssen’s “OxyContin Backgrounder” sales training aid. In response to the prompt “Give an advantage of Duragesic over Oxycontin as it relates to addiction?,” the Backgrounder

⁷¹³ JAN-MS-00306124 at 12, 13.

⁷¹⁴ JAN-MS-00306124 at 39.

⁷¹⁵ JAN-MS-02338206 at 50 (PSUR for April 2000 to April 2001, showing 155 cases of abuse or addiction, including 50 which resulted in death); JAN-MS-00911743 at 13, 43 (PSUR for April 2001 to April 2002, showing 144 cases of abuse or addiction, including 20 which resulted in death); JAN00221849 at 48-49 (PSUR for April 2002 to April 2003, showing 134 cases of abuse or addiction, including 55 which resulted in death).

states “Potentially, less street value, toxic when crushed,” but then notes “Consider rewording this question, Duragesic can be chewed.”⁷¹⁶

351. Janssen also acknowledged the lack of data supporting its lower abuse claims in a memorandum reporting on an August 14, 2001 meeting to discuss an upcoming FDA advisory board regarding OxyContin abuse issues. The memorandum listed objectives for the FDA meeting, including “to help protect the class from restrictive actions that would further hinder proper patient care, or in a sense defend the class.”⁷¹⁷ In response to another objective, “To actively differentiate Duragesic from oral formulations and Oxycontin, and position ourselves as an alternative with potentially less abuse potential,” Pamela Rasmussen inserted “I think there’s another option: Advocate for aggressive treatment of pain, defend the class and ‘mention’ that there are multiple types and formulations of opioids, which have different safety/benefit profiles -- including the product that has shaped our own involvement in the field, Duragesic....The Key is not to turn this into a promotional platform (especially since I don’t think we have enough data to back up our less abuse claim).”⁷¹⁸

352. A similar recognition of lack of support for its lower abuse claim is seen in the company’s November 30, 2001 Executive Summary for Chronic Pain Scientific Advisory Board, which discussed messages relating to the abuse potential of Duragesic, including “DURAGESIC provides pain relief in sustained-release transdermal formulation and has a reported rate of abuse between 0 and 0.1%.”⁷¹⁹ However, the Summary noted in regards to this message the “Continued rejection of the DAWN data and abuse statistics,” and acknowledged a lack of knowledge and

⁷¹⁶ JAN-MS-02727830 at 2.

⁷¹⁷ JAN-MS-00899138 at 2.

⁷¹⁸ JAN-MS-00899137; JAN-MS-00899138 at 2.

⁷¹⁹ JAN-MS-00782617 at 7.

data about the abuse potential for Duragesic patients with no history of substance abuse.⁷²⁰ The Summary made the “Conclusion: Do not include the abuse message. Do not sell opioids on the abuse issue.”⁷²¹

353. Yet Janssen continued to promote Duragesic as having a lower risk of abuse than OxyContin. Sales training materials from August 2001 provide examples of how Duragesic sales representatives could respond to doctors raising abuse related to OxyContin, including the statement that “due to the technology of the patch delivery system many pain specialists believe that Duragesic has less potential for abuse.”⁷²²

354. In 2002 Janssen provided a \$50,000 grant to the American Pain Foundation for a patient education brochure which stated that “there is little risk of addiction” with opioids when taken as properly prescribed and directed, “unless you have a history of substance abuse.”⁷²³ The brochure also stated that “physical dependence—which is not addiction...” usually is not a problem if you go off your medications gradually.”⁷²⁴

355. In its March 2000 warning letter discussed above, DDMAC also found that Janssen’s claim of “Low abuse potential!” in the homemade piece at issue was false or misleading because it suggested that “Duragesic has less potential for abuse than other currently available opioids” without substantial evidence.⁷²⁵ DDMAC further noted that “this claim is contradictory to information in the approved product labeling (PI) that states, ‘Fentanyl is a

⁷²⁰ *Id.*

⁷²¹ *Id.*

⁷²² JAN-MS-00313051 at 2.

⁷²³ JAN-MS-00723779; JAN-MS-00788087; ABT-MDL-KY-0025968. The company described this grant internally as “a verbal commitment; nothing was put in writing.” JAN-MS-00723779.

⁷²⁴ ABT-MDL-KY-0025968 at 3.

⁷²⁵ JAN-MS-00238338 at 2.

Schedule II controlled substance and can produce drug dependence similar to that produced by morphine.”⁷²⁶ DDMAC also found that Janssen failed to present any risk information concerning warnings, precautions, side effects or contraindications, and thus the piece was “lacking in fair balance.”⁷²⁷

356. In its 2004 warning letter regarding a Janssen professional file card described above, DDMAC also found that the file card made unsubstantiated claims of lower abuse than other opioids. DDMAC found that relying on the reported rate of mentions in DAWN data was misleading because Duragesic was not as widely prescribed as other drugs.⁷²⁸

357. The DDMAC letter prompted Janssen executive Scott Reines to write Janssen VPs regarding the letter, stating, “not as egregious as the Risperdal situation, but there is plenty of evidence that our promotional material is not being adequately self-regulated.”⁷²⁹

358. An April 2006 letter to Janssen from FDA commented on Janssen’s Duragesic risk management plan and requested that Janssen “provide the definition and criteria used to identify adverse event reports related to addiction, as well as a list of adverse event terms that are coded under the term ‘addiction,’” “list adverse event terms that are coded under ‘misuse’ and ‘abuse,’” and “emphatically state that Duragesic should not be used in opioid naïve patients.”⁷³⁰

359. FDA’s letter prompted Janssen Therapeutic Area Manager Dawn Sanderson-Bongiovanni, PharmD, to write Dr. Bruce Moskovitz, Janssen Therapeutic Area Head for Analgesia & GI. Dr. Sanderson-Bongiovanni noted that she was researching concerns raised by

⁷²⁶ *Id.* at 2.

⁷²⁷ JAN-MS-00238338 at 4.

⁷²⁸ JAN-MS-00779345.

⁷²⁹ JAN-MS-02478753.

⁷³⁰ JAN-MS-00480894 at 1-2.

FDA in its response to Janssen's Duragesic RiskMap proposal, and asked if Dr. Moskowitz could "site [sic] a 'landmark' article that reflects current medical thinking about the occurrence and etiology of addiction (induced by opioid therapy)?"⁷³¹

360. Dr. Moskowitz forwarded the request to Dr. Vorsanger and Dr. David Hewitt, a neurologist in the analgesia group, stating "pain and addiction are not my specialty."⁷³² Dr. Hewitt responded that "*the evidence supporting the low abuse potential among patients receiving opioids for chronic pain is not based upon strong data*. Margo McCaffery discusses <1%. I have seen numbers that suggest the rate of addiction is similar to the population at large and no higher."⁷³³

361. Dr. Vorsanger responded to Dr. Hewitt, "I am skeptical of the low rates that Margo and others cite. Remember, rates of addiction for non-opioid substances such as alcohol are much higher (rates of 5-8% or even higher have been quoted for the general population)."⁷³⁴ In his deposition, Dr. Moskowitz agreed, testifying that studies on iatrogenic addiction with chronic pain patients provide "a potentially inaccurate estimate, it may underestimate the rate of abuse, misuse, and diversion. And particularly addiction and those reports of addiction."⁷³⁵

362. In the period prior to the exchange above between Janssen clinical executives and the introduction of the first generic version of Duragesic in early 2005, Janssen reported over 300 annual adverse events involving abuse or addiction with the drug for April 2003 to April 2004,⁷³⁶

⁷³¹ JAN-MS-00957863 at 2.

⁷³² JAN-MS-00957863 at 1.

⁷³³ *Id.* (emphasis added).

⁷³⁴ *Id.*

⁷³⁵ Moskowitz Dep. 695:2-700:21, November 14, 2018 (testifying regarding the exchange between himself, Dr. Vorsanger, Dr. Hewitt, and Dr. Sanderson-Bongiovanni in JAN-MS-00957863).

⁷³⁶ JAN00221868 at 128.

and over 400 for April 2004 to April 2005⁷³⁷. In the latter period the adverse events included 76 which resulted in death.⁷³⁸

363. Janssen's sales call notes indicate that it was frequently promoting Duragesic on the basis that DAWN data showed it had low abuse rates.⁷³⁹ For example, a April 21, 2004 call note stated "Showed him the DAWN data and how Dur[agesic] is very low abuse potential"⁷⁴⁰ and an August 11, 2004 note stated "...thought that dur[agesic] was highly abusable. Presented DAWN data for low abuse potential."⁷⁴¹

364. Sales call notes also show that Janssen marketed Duragesic to nursing home residents from 1998 on the basis of low abuse potential, quality of life and convenience.⁷⁴²

365. In my opinion, Janssen misleadingly promoted Duragesic as having no or lower abuse potential, particularly compared with OxyContin, without substantial evidence.

5. Janssen Made Shifting and Unsubstantiated Claims Regarding the Abuse Potential of the Reservoir v. Matrix Formulations of Duragesic as the Sales Environment for the Drug Shifted.

366. Janssen's Duragesic system approved in the United States in 1990 was a "reservoir" patch system that "utilized a form-fill-seal design: a drug reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose that delivers fentanyl to the skin across a rate-controlling membrane."⁷⁴³

⁷³⁷ JAN-MS-00553427 at 138.

⁷³⁸ JAN-MS-00553427 at 22.

⁷³⁹ See JAN-OH-00000005, JAN00118955.

⁷⁴⁰ JAN00118956.

⁷⁴¹ JAN00118955.

⁷⁴² JAN-OH-00000004.

⁷⁴³ Jan-MS-00386726 at 3.

367. From 1993 through 2004, Janssen's sales of Duragesic totaled over \$6 billion.⁷⁴⁴

368. In November 2003, FDA approved a generic version of the Duragesic patch made by Mylan that used a different design called matrix.⁷⁴⁵ Matrix-designed products consist of an entirely solid material in which fentanyl is embedded in a layer of adhesive.⁷⁴⁶ Janssen's sales dropped from a high of over \$1 billion in 2004 to over \$600 million in 2005, the first year the Mylan generic patch was sold, and dropped further to just under \$400 million in 2006.⁷⁴⁷

369. In 2001, Janssen had considered moving from its Duragesic reservoir to a matrix formulation (then referred to by Janssen as "D-TRANS"),⁷⁴⁸ and had commissioned a report from Pinney Associates entitled "D-TRANS Fentanyl: Summary of Benefits and Risks: Abuse and Diversion."⁷⁴⁹ The Pinney report noted that potential "areas of vulnerability" of the new matrix formulation included that it "contains theoretically higher amounts of divertible drug compared to the existing formulation" and "is potentially subject to extraction approaches that would be considered acceptable to drug abusers and illicit drug distributors."⁷⁵⁰

370. The Pinney report concluded that while the matrix formulation was "approvable," the fact that it "will contain substantially more potentially abusable fentanyl in both the unused and used systems," and the environment of heightened regulatory scrutiny, "will almost certainly lead to a very critical review which could lead to significant threats to approval, limitations on

⁷⁴⁴ PPLP003364349.

⁷⁴⁵ FDA letter to Mylan Technologies, June 22, 2004, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2004/76-258.rescind.ltr.pdf (last visited March 20, 2019).

⁷⁴⁶ JAN-MS-00386726 at 3.

⁷⁴⁷ PPLP003364349.

⁷⁴⁸ Moskowitz Dep. 160:15-24, November 13, 2018.

⁷⁴⁹ JAN-MS-02119824.

⁷⁵⁰ *Id.* at 6.

marketing, and stronger misuse/abuse ‘detering’ labeling.”⁷⁵¹ Janssen did not seek approval of a matrix formulation at that time.

371. While sales of the generic Mylan matrix product approved in 2003 were delayed until early 2005 due to patent litigation,⁷⁵² Janssen set in motion plans to counter competition from it in the meantime. A Duragesic Business Update from January 2004 concerned selecting a “viable strategy to protect current asset: protect against AB [generic equivalency] rating”⁷⁵³ and meeting an objective to “establish differentiation between reservoir and matrix technology in a timely manner (AB rating).”⁷⁵⁴

372. The “optimal strategy” identified in the 2004 Business Update was “different dosage forms,” for which “key tactics” included conducting abuse liability studies to show “ease of extraction” and “attractiveness (from abuser’s perspective)” of matrix compared to reservoir, and filing a Citizen’s Petition with the FDA.⁷⁵⁵

373. In a section entitled “Defend Current Asset,” the Business Update included advertisements with the tagline “Confidence, Interrupted”—a play on Duragesic’s existing tagline of “Life, Interrupted.”⁷⁵⁶ These ads questioned whether matrix was a true generic equivalent, despite FDA’s approval of it as such, and contained comparative abuse liability claims such as “The Matrix Fentanyl Deliver System is an attractive target for diversion,” “The Matrix Fentanyl Deliver System: Why Take the Chance of Abuse and Diversion?,” and “The

⁷⁵¹ *Id.* at 5, 7.

⁷⁵² FDA letter to Mylan Technologies, June 22, 2004, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2004/76-258.rescind.ltr.pdf (last visited March 20, 2019)

⁷⁵³ JAN-MS-02396626 at 2.

⁷⁵⁴ *Id.* at 10. At the same time, Janssen explored options for partnering “with a generic company to retain as much of the Fentanyl reservoir market share as possible.” *Id.* at 32, 34.

⁷⁵⁵ *Id.* at 12, 24, 72.

⁷⁵⁶ *Id.* at 62-66.

Matrix Fentanyl Deliver System: A Threat to Patient and Public Safety?”⁷⁵⁷ Another ad in the Update claimed that matrix “encourages drug-seeking behavior.”⁷⁵⁸ The ads further raised the specter of “increased liability of health care providers” and suggested that prescribing Duragesic could avoid same.⁷⁵⁹

374. Also in January 2004, Janssen developed a script and materials for its sales force to use in persuading physicians to prescribe its reservoir Duragesic patch over the generic matrix patch.⁷⁶⁰ Like the ads in the Business Update, these promotional materials emphasized a claimed greater risk of misuse and abuse with matrix than with Duragesic. For example, the script claimed that “the differences between the matrix and the DURAGESIC reservoir can put your patients and the public at risk,” and that matrix “falls far short of the high public safety standard of DURAGESIC.”⁷⁶¹ It asserted that with matrix fentanyl could “be easily extracted from the patch by chewing, soaking, or other means-thus creating the potential for a real public safety problem” and that “matrix can also be cut into smaller pieces-another risk to public safety.”⁷⁶²

375. The script invoked DAWN data to claim that “Duragesic is not attractive to abusers,” and asserted that Duragesic had “an extremely low rate of abuse.”⁷⁶³ As noted above, by this time Janssen had been warned by DDMAC about misleading marketing claims regarding

⁷⁵⁷ *Id.* at 30-31, 62-66.

⁷⁵⁸ *Id.* at slide 31.

⁷⁵⁹ *Id.* at slide 31, 64, 66; The Business Plan Update also shows that Janssen planned to continue “‘aggressive’ sales force promotion through 2004” with “high-frequency” calls to current Duragesic prescribers and “high-volume pharmacies,” and to “align incentive compensation” to “minimize erosion.” *Id.* at 27. A March 2004 “Duragesic Contingency Plan Update” similarly shows Janssen planned to “focus on high-volume MDs and pharmacists” and “target top Duragesic writers” for sales calls prior to the launch of Mylan’s generic matrix. JAN-MS-02990985 at 13, 17.

⁷⁶⁰ JAN-MS-00724843.

⁷⁶¹ *Id.* at 1, 4.

⁷⁶² *Id.* at 2.

⁷⁶³ *Id.* at 7.

Duragesic's low abuse potential, and was aware of DAWN's limits in accurately measuring abuse. Also as noted above, by this time Janssen had reported in its PSURs for Duragesic over 544 cases involving drug abuse or addiction, over 125 of which resulted in death.

376. The script further claimed that reservoir Duragesic would "protect[] you and your liability in prescribing."⁷⁶⁴ It went on to assert that each matrix patch could cause an abuse epidemic and harm patients with chronic pain by limiting their access to medication:

So if the wrong person gets their hands on one of these new matrix systems, they are looking at the equivalent of between 100 and 200 tablets of oxycodone. If they get a whole box, just think of how much more that is. *And how many people that could affect.* As we've seen with oxycodone, this is exactly what abusers are looking for-a delivery system that both contains a lot of drug and can be easily defeated to get a quick high. Each one of these little matrix systems contains all the potential for another epidemic-which means another crisis not only for the public, but for prescribers as well. Furthermore, it could negatively impact patients with chronic pain by limiting access to the effective pain therapy they legitimately need.⁷⁶⁵

377. The script concluded that "this new 'generic' matrix system isn't really a generic at all-it is a completely different system, and one that could pose a great threat to you, your patients, and the public at large" and that these risks could be avoided by prescribing Duragesic instead.⁷⁶⁶

378. Yet, Janssen itself launched a fentanyl matrix patch in Europe in 2004, called D-Trans, the same year it prepared the Business Update and script above.⁷⁶⁷ In 2003, in preparation for this launch, Janssen had prepared an "assessment of the potential for prescription analgesic

⁷⁶⁴ *Id.* at 3.

⁷⁶⁵ *Id.* at 5-6 (emphasis in original).

⁷⁶⁶ *Id.* at 8; Janssen's testing of the messages contained in the ads and sales script indicated they made doctors more likely to increase prescriptions of Duragesic and to "attempt to ensure that patients received the Duragesic brand," based in part on "the potential difference in abuse potential." JAN-MS-02391035 at 47-50. Janssen projected a positive ROI [return on investment] of \$100-150 million in 2005 as a result. *Id.* at 50.

⁷⁶⁷ JAN-MS-02135033 at 2.

abuse, misuse and diversion in Europe.”⁷⁶⁸ Janssen reported that the abuse expert consulted for the assessment opined that “there is no evidence that prescribed opioids are abused to a significant extent” and “fentanyl is not an attractive compound for drug addicts.”⁷⁶⁹ Contrary to Janssen’s dire warnings in the documents above, the expert found it “highly unlikely” in the European context that the matrix system would “trigger more significant diversion” than the existing reservoir system.⁷⁷⁰

379. While Janssen would later reverse itself and adopt the position of its European expert as to the United States also, *see infra*, in June 2004, shortly after its matrix was approved in Europe, it received a draft of an update it had commissioned of the 2001 Pinney report discussed above, entitled “Assessment of Abuse Potential of the Matrix Formulation of Fentanyl Transdermal System: Update of the 2001 Pinney Associates’ Report.”⁷⁷¹ Echoing the promotional messages in the sales script and ads above, the assessment found that “availability of a matrix formulation ... would be expected to increase the rates of abuse because of the ability to more easily abuse and/or divert drug by cutting a matrix ... into smaller unit doses or extracting it from the matrix technology,” and “might fuel” new types of abuse.⁷⁷² It further noted that “it is plausible that US regulatory agencies would have appropriately greater concerns than their colleagues in many other countries in Europe...”⁷⁷³

380. The assessment concluded that “a matrix [fentanyl patch] should not, and more likely cannot, be marketed without a strong RiskMAP that provides evidence-based elements or

⁷⁶⁸ JAN-MS-01200052.

⁷⁶⁹ *Id.* at 7.

⁷⁷⁰ *Id.* at 8.

⁷⁷¹ JAN-MS-02119824.

⁷⁷² *Id.* at 38.

⁷⁷³ *Id.* at 4.

tools to minimize abuse and diversion and enable rapid detection of abuse and diversion that would occur.”⁷⁷⁴

381. A few months earlier, in February 2004, Dr. Moskovitz wrote to an executive at Mudskipper Strategies regarding abuse studies Janssen was “embarking on” to “differentiate Duragesic (reservoir) from the ‘unprotected’ matrix patch.”⁷⁷⁵ Dr. Moskovitz explained to the Mudskipper executive that Janssen had identified a series of such studies a year prior for comparing AP-48, Janssen’s planned new version of Duragesic with naltrexone, to generic matrix, but that since AP-48 was “delayed significantly” the focus was now on comparing the reservoir Duragesic on the market to matrix instead.⁷⁷⁶ Dr. Moskovitz noted that he anticipated that a “white paper” based on the studies would be used to “‘paint’ a full picture of risks associated with the matrix patch.”⁷⁷⁷ As noted above, abuse liability studies were identified as a “key tactic” to differentiate matrix from Duragesic reservoir for marketing purposes in the 2004 Business Update.⁷⁷⁸

382. In September 2004, a few months after receiving the Pinney Associates Assessment described above, Dr. Moskovitz gave an internal presentation on comparative abuse liability studies Janssen had conducted of reservoir and matrix.⁷⁷⁹ His conclusions and recommendations based upon those studies were closely similar to those in the Pinney Associates Assessment, and included “Fentanyl matrix patches may increase safety risk in real-

⁷⁷⁴ *Id.* at 38.

⁷⁷⁵ JAN-MS-01196462. Mudskipper “acted for [Janssen] in collating all of the information that [Janssen] collected over the course of 2003-2004 relative to...questions about the relative benefits and risks of the Duragesic reservoir or matrix.” Moskovitz Dep. 162:3-17, November 13, 2018.

⁷⁷⁶ *Id.*

⁷⁷⁷ *Id.*

⁷⁷⁸ JAN-MS-02396626 at 12.

⁷⁷⁹ JAN-MS-00478361.

world usage,” “Fentanyl matrix patches may present increased societal risk,” and “Stringent risk management programs should be mandatory for fentanyl matrix patches.”⁷⁸⁰

383. Later that month Dr. Moskovitz wrote to other Janssen executives regarding the studies:

We believe the FDA will consider these studies supportive of our position that the reservoir patch and matrix patch should be considered two different formulations and, therefore, not be A/B rated (interchangeable at the pharmacy). This lack of interchangeability would have a huge impact in the market... The data will also be of significant interest to healthcare providers and inform them of the potential risks for not writing Do Not Substitute.”⁷⁸¹

384. Dr. Moskovitz additionally stated in his email, “We believe the data will lead many HCPs to prescribe Duragesic with instructions Not to Substitute.”⁷⁸²

385. The “white paper” prepared for Janssen by Mudskipper Strategies regarding the abuse studies, anticipated by Dr. Moskovitz’s February 2004 email, arrived September 22, 2004.⁷⁸³ Again echoing the marketing messages described above, it found that “Fentanyl matrix patches are more attractive to potential abusers than DURAGESIC® reservoir patches,” that “availability of a fentanyl matrix patch is likely to increase the diversion of patches with major public health consequences,” and that “the abuse potential for a fentanyl matrix patch is significantly higher than that of the DURAGESIC® reservoir patch.”⁷⁸⁴

386. The white paper’s conclusions also included “manufacturers of fentanyl matrix patches should be required to implement stringent and comprehensive risk management surveillance and intervention programs for their products,” “Given the substantial differences in

⁷⁸⁰ *Id.* at slides 43, 44.

⁷⁸¹ JAN-MS-00482680 at 3.

⁷⁸² *Id.* at 1.

⁷⁸³ JAN-MS-00617066.

⁷⁸⁴ *Id.* at 84-85.

risks for abuse and misuse...the DURAGESIC reservoir patch and fentanyl matrix patches should not be considered interchangeable,”⁷⁸⁵ and “Fentanyl matrix patches present an unacceptable additional risk both to patient safety and public health in the U.S.”⁷⁸⁶

387. On November 12, 2004, Janssen, through Alza, filed a Citizen’s Petition with the FDA that made the same arguments as in the white paper it commissioned. Janssen’s Petition requested that the FDA take action against manufacturers of fentanyl matrix delivery systems to “reduce the potential for abuse of certain types of these products.”⁷⁸⁷ Specifically, the Petition urged FDA to: 1) “require manufacturers of fentanyl matrix systems to develop and implement comprehensive risk minimization programs that successfully address the specific issues presented by their products” and 2) “classify matrix and reservoir fentanyl transdermal systems as different dosage forms...that are not pharmaceutical equivalents.”⁷⁸⁸ The latter action would mean reversing FDA’s decision to give Mylan’s generic matrix patch an AB-rating, an action which Dr. Moskovitz had previously stated “would have a huge impact in the market,” as noted above.

388. Janssen argued these actions were called for because “(1) matrix systems can be cut into small pieces, and (2) fentanyl is more easily extracted under certain conditions from a matrix product than from a reservoir system, matrix systems present a different and possibly larger potential for abuse in the United States compared to the Duragesic® reservoir system,”

⁷⁸⁵ *Id.* at 84-85.

⁷⁸⁶ *Id.* at 12.

⁷⁸⁷ JAN-MS-00386726.

⁷⁸⁸ *Id.*

citing as support one of the abuse studies it had commissioned earlier in the year to differentiate reservoir from matrix.⁷⁸⁹

389. FDA rejected Janssen's Citizen Petition on January 28, 2005.⁷⁹⁰ FDA found that reservoir and matrix were pharmaceutically equivalent under its rules and past practices.⁷⁹¹ As to Janssen's argument that matrix would be more prone to abuse, FDA stated, "we believe that both the reservoir and matrix fentanyl transdermal systems have the potential to be abused, and petitioners have not presented data sufficient to persuade us that matrix products have a greater abuse liability potential than reservoir ones. We find that theoretical differences in potential abuse liability are not sufficient to reclassify [matrix]."⁷⁹²

390. In addition, FDA found the abuse study Janssen submitted to be "flawed because... 'the researchers note that nearly a quarter of [persons sampled] claimed experience with the fentanyl matrix patch, which was not available.'"⁷⁹³ FDA also noted that the "statistical validity of the "Opioid Attractiveness Scale" and of the sample size used for [Janssen's] study has not been demonstrated."⁷⁹⁴

⁷⁸⁹ *Id.* at 2, 5. Janssen cast the fact that it was itself marketing matrix in Europe as a source of credibility, instead of as an inconsistency, and argued that "the environment regarding prescription drug abuse in Europe differs from that in the US." *Id.* at 7, n.6). However, Janssen formulated messages to use in response to European inquiries regarding its attempt to block an equivalent matrix product in the U.S. partly on the grounds of it being more prone to abuse. JAN-MS-00891010.

⁷⁹⁰ JAN-MS-00950449.

⁷⁹¹ *Id.* at 3-4.

⁷⁹² *Id.* at 6.

⁷⁹³ *Id.* at 7.

⁷⁹⁴ *Id.* at 7.

391. FDA granted final approval to Mylan's generic matrix patch on February 2, 2005.⁷⁹⁵

392. In early 2008, FDA required that Janssen issue a recall of its Duragesic patches due to manufacturing issues.⁷⁹⁶ In January 2008, Ravi Desiraju, Janssen's Clinical Director and Team Leader for Duragesic, wrote to Dr. Moskowitz, asking, "with these problems with the reservoir patches (cut patches, fold-overs) will we be better off with matrix patches?"⁷⁹⁷ A discussion over email ensued between Desiraju, Dr. Moskowitz, and Scott Trembley, Product Director-Established Products, about whether there was more diversion with matrix than reservoir, and whether obtaining matrix approval would involve delays.⁷⁹⁸ Trembley raised reviving the AP-48 (Naltrexone matrix) program as an alternative, to which Desiraju responded that AP-48 was terminated due to negative outcomes in a pivotal clinical study, and he was "raising the reservoir/Matrix issue in light of the manufacturing problems we are currently having."⁷⁹⁹

393. On March 11, 2008, Desiraju reported to Steven Silber, Vice President – Established Products, on Janssen's consideration of developing a matrix patch, noting that Janssen had filed a Citizen Petition requesting FDA not approve generic matrix a few years earlier.⁸⁰⁰ Desiraju wrote, "In light of this history, the team felt that we should first investigate if the rate of abuse with the matrix formulation is any higher than the reservoir product," and that

⁷⁹⁵ FDA Clears Generic Version of Pain Patch (February 2, 2005). available at <https://www.webmd.com/pain-management/news/20050202/fda-clears-generic-version-of-pain-patch-news> (last visited March 20, 2019)

⁷⁹⁶ JAN-MS-00747681.

⁷⁹⁷ JAN-MS-02007690 at 3.

⁷⁹⁸ *Id.*

⁷⁹⁹ *Id.* at 1.

⁸⁰⁰ JAN-MS-00351356.

Dr. Moskowitz had therefore contacted Rick Dart of the RADARS surveillance group, who advised that “both reservoir and matrix are abused to a similar extent” and “he is not aware of any differences between the two,” though “his surveillance program is not sensitive enough to pick up any differences....”⁸⁰¹

394. On March 21, 2008, Janssen had a teleconference with FDA regarding recent recalls of its Duragesic patches.⁸⁰² As Dr. Moskowitz summarized in a March 23, 2008, email to other Janssen executives, “FDA made clear they would not allow for another recall of the type we had in 2004 and earlier this year. They indicated they would urge we move to an alternative formulation (matrix being the only viable option at the moment), but were open to learning more about our decisions in 2000 and 2004 to remain with the reservoir and review data we will submit for abuse and diversion of the reservoir and matrix. While we may ultimately decide to proceed with development of a matrix formulation for the US, we must proceed with an open mind to evaluate the data for risks of abuse and diversion, as well as risks for patient exposure from a manufacturing defect.”⁸⁰³

395. On April 24, 2008, a RADARS report for Janssen found that “RADARS System data indicate that all patch formulations show evidence of abuse, misuse and diversion.”⁸⁰⁴ Dr. Moskowitz forwarded it to Desiraju the next day in an email that backtracked on his earlier research, showing that Janssen had come full circle on matrix since vigorously opposing its approval on safety grounds in 2004.⁸⁰⁵ Dr. Moskowitz’s email stated that based upon the

⁸⁰¹ *Id.*

⁸⁰² JAN-MS-02005184.

⁸⁰³ *Id.*

⁸⁰⁴ JAN-MS-01200481.

⁸⁰⁵ JAN-MS-01200479.

RADRARS data he had concluded that “there is insufficient evidence...to suggest that levels of abuse and diversion of the matrix...patches are substantially higher than those for reservoir patches, and that lacking such data, J&J feels comfortable that we would not be increasing risks to patients if we develop a matrix patch.”⁸⁰⁶

396. Janssen followed through by submitting an NDA for approval of a Duragesic matrix formulation in the U.S. on January 30, 2009.⁸⁰⁷ The marketing plan Janssen submitted to FDA in March, 2009 indicated that it would cease shipping Duragesic reservoir patches once the matrix patch was approved.⁸⁰⁸ Final approval was granted on July 31, 2009.⁸⁰⁹

397. A Janssen “Media Messages” primer regarding the transition from reservoir to matrix, dated April 21, 2009 and labeled for “reactive use only,” explained that the change was happening because “After several years of making both a reservoir and a matrix patch globally, and after continued surveillance, the company determined that our initial concerns about risk of abuse of the matrix-style patch in the United States have not materialized.”⁸¹⁰

398. In response to questions regarding why Janssen had changed its position on matrix since its 2004 Citizen Position, the Media Messages primer instructed to respond, “At that time we were concerned about possible risks of diversion and abuse in the United States with the matrix-style patch. Since then, active surveillance of current safety data shows no abnormally

⁸⁰⁶ *Id.*

⁸⁰⁷ JAN-MS-04230555.

⁸⁰⁸ JAN-MS-00885848.

⁸⁰⁹ JAN-MS-00292753.

⁸¹⁰ JAN-MS-01250151 at 2.

high level of abuse or diversion in the United States for currently marketed fentanyl matrix systems.”⁸¹¹

399. On December 1, 2009, four months after Duragesic matrix was approved, FDA advised Janssen that “there were growing concerns within the agency regarding the residual content in the DURAGESIC matrix patch--70% more residual fentanyl in the matrix patch compared to reservoir,” and that its concerns “were related to potential misuse, abuse, disposal and exposure into the water.”⁸¹² FDA requested that Janssen “consider developing a new Duragesic patch formulation to minimize the residual fentanyl,” and stated...“We know that it is technically feasible.”⁸¹³

400. Janssen responded to FDA that it would conduct feasibility studies “to determine if we can lower the fentanyl amount using the current Duragesic Matrix formulation.”⁸¹⁴ Janssen conducted such studies and advised FDA in 2016 that it would be seeking supplemental approval for a reformulated matrix with reduced residual fentanyl, but that it “does not have data to demonstrate that the new formulation with lower residual content would decrease the risk of abuse, addiction, or life-threatening/fatal outcomes in case of accidental exposure.”⁸¹⁵

401. In my opinion, Janssen made misleading, unsubstantiated and shifting claims regarding the abuse potential of the reservoir v. matrix formulations of Duragesic as the sales and regulatory environment changed.

⁸¹¹ *Id.* at 3. In August 2009, Lori Lonczak, head of Marketing, Pain Franchise, asked Scott Trembley, Marketing/Commercial Leader for Duragesic, to send a voicemail to sales representatives about the formulation change. JAN-MS-00280657. Trembley noted “I would STRONGLY encourage no proactive communication by the field...,” in part because “it could create a question as to our 2004 position on a matrix vs. today. A key Duragesic prescriber could surface all the issues above.” *Id.* at 2.

⁸¹² JAN-MS-02410536.

⁸¹³ *Id.*

⁸¹⁴ JAN-MS-00888210.

⁸¹⁵ JAN-MS-00587189 at 7, 13.

402. In my opinion, Janssen's promotion of Duragesic understated its risks and overstated its benefits, and was false and misleading.

C. Nucynta

403. Nucynta is the brand name for tapentadol, an opioid analgesic marketed by Janssen, a Johnson & Johnson company, from 2009 until 2015.⁸¹⁶

404. Tapentadol's exact mechanism of action is unknown, but it is believed to derive from its mu-opioid agonist activity and inhibition of norepinephrine reuptake.⁸¹⁷

405. Nucynta was first approved by FDA in immediate-release form as Nucynta IR in November, 2008,⁸¹⁸ for relief of moderate to severe acute pain in patients 18 years of age or older.⁸¹⁹ Sales began in June 2009.⁸²⁰

406. An extended-release form, Nucynta ER, was approved by FDA in August, 2011,⁸²¹ for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.⁸²²

407. In August, 2012, neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults was added to the indication for Nucynta ER, also for when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.⁸²³

⁸¹⁶ In this report, "Janssen" refers to all Johnson & Johnson companies and their predecessors, successors and affiliates involved in the manufacturing, marketing and promotion, and sale of Nucynta IR and Nucynta ER, including Defendants Janssen Pharmaceutica, Inc. N/K/A Janssen Pharmaceuticals, Inc.; Janssen Pharmaceuticals, Inc.; Johnson & Johnson; and Ortho-Mcneil- Janssen Pharmaceuticals, Inc. N/K/A Janssen Pharmaceuticals, Inc., as well as Alza Corporation and Pricara.

⁸¹⁷ Nucynta IR label, November, 2008, JAN-MS-00445032; Nucynta ER label, August, 2011, JAN-MS-02544901.

⁸¹⁸ JAN-MS-01130740

⁸¹⁹ Nucynta IR label, November, 2008, JAN-MS-00445032

⁸²⁰ JAN-0014-0021012

⁸²¹ Nucynta ER Approval letter, August 25, 2011, JAN-MS-00214315

⁸²² Nucynta ER label, August, 2011, JAN-MS-02544901

408. After \$1 billion in Nucynta IR and ER sales through 2014,⁸²⁴ Janssen sold the rights to Nucynta IR and ER to Depomed in 2015, for \$1.05 billion.⁸²⁵

409. As discussed below, the marketing messaging utilized by Janssen to promote Nucynta, like those developed by Purdue for OxyContin, overstated its benefits and understated its risks, but also sought to distinguish Nucynta from OxyContin/oxycodone in order to claim market share.

1. Janssen’s Marketing Strategy for Nucynta

(a) Covering Acute to Chronic Continuum

410. Nucynta represented Johnson & Johnson’s and Janssen’s entry into the oral opioids market. It also represented the first “new molecule” centrally-acting opioid analgesic in 25 years, as Janssen’s marketing materials asserted.⁸²⁶

411. From the outset, Janssen planned to introduce both IR and ER formulations of Nucynta, with their anticipated approvals about one year apart.⁸²⁷ They were both addressed in the same pre-launch business plans,⁸²⁸ in which Janssen discussed how the IR formulation would pave the way for the subsequent adoption of the ER formulation by prescribers, allow for coverage of the full spectrum of pain from acute to chronic in one molecule, and thereby give the drug a competitive advantage against OxyContin/oxycodone:

⁸²³ Nucynta ER Supplemental Approval Letter, August 28, 2012, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/200533Orig1s001ltr.pdf (last visited March 20, 2019)

⁸²⁴ PPLP003364349.

⁸²⁵ JAN-MS-00264775.

⁸²⁶ JAN-MS-00477361 at 4.

⁸²⁷ JAN-MS-00477361 at 4.

⁸²⁸ JAN-MS-00443233 (“Tapentadol Business Plan 2008,” dated September 2007); JAN-MS-00477361 (“2009 Tapentadol Business Plan Situation Assessment,” dated June 2008); JAN-MS-00350627 (“Nucynta (IR and ER) 2010 Business Plan,” dated May 2009).

411.1. In its 2008 Business Plan for Tapentadol, Janssen set out a “Market Strategy” timeline to “accelerate adoption” in which it would “Generate successful experience with IR in 2009,” and then “Drive ER adoption leveraging clinical success with IR” in 2010.⁸²⁹

411.2. In its 2009 Tapentadol Business Plan, Janssen noted that “Back and Neck patients are the “sweet-spot” and the common path between IR to ER.”⁸³⁰

411.3. The same 2009 Business Plan described a “Tapentadol ER and IR US Market Strategy” to “Generate rapid adoption of IR rationalizing first choice use and pave the market introduction of the ER formulation.”⁸³¹

411.4. Janssen’s 2010 Nucynta IR and ER Business Plan contained a slide entitled “Message Strategy Evolution,” which showed its promotional messaging strategy dovetailing with the introduction of IR and then ER. It noted “Benefits of IR to ER transition vs Oxy.”⁸³²

411.5. Another “Message Evolution” slide in the 2010 Business Plan showed that in 2010 Janssen would “Build on SAO [short acting opioids] Experience” with Nucynta IR to “Replace OxyContin;” in 2011 it would “Expand to Broad Chronic Pain Types” to “Continue to Replace Oxy;” and in 2012 it would achieve a “Foundation of Management for both SAO and LAO to include the full spectrum of pain.”⁸³³

⁸²⁹ JAN-MS-00443233 at 13.

⁸³⁰ JAN-MS-00477361 at slide 12.

⁸³¹ *Id.* at slide 27.

⁸³² JAN-MS-00350627 at slide 34.

⁸³³ *Id.* at slide 38.

411.6. In the same Business Plan, Janssen identified “Evolve the value discussion to displace the oxycodone molecule” as a “Strategic Driver” of growth, and “Own the tapentadol patient from IR to ER (patient continuum)” (emphasis added) as the corresponding “Executorial Driver.”⁸³⁴

411.7. In its 2011 Nucynta ER Launch Plan, Janssen noted that “Introduction of ER expands NUCYNTA molecule to compete in total moderate to severe pain market.” The slide showed that Janssen anticipated a total of 70 million prescriptions between IR and ER, and quoted a prescriber as stating, “The (acute/chronic) lines blur because of the ‘acute on chronic’ situation.”⁸³⁵

412. Janssen’s launch plans noted that acute pain can lead to chronic pain, and sought to leverage this through offering the two Nucynta formulations, IR and ER. In Janssen’s April 2009 “Market Overview Strategic Plan,” a slide entitled “Tapentadol – Pain Management Success Redefined” indicated that “Under-Management Driven by Side Effects” leads to “Severe Consequences,” causing a progression from “Acute pain to Chronic Pathology.” The slide also showed “Tapentadol IR—Redefines Pain Outcomes” leading to “Tapentadol ER—Optimizes Pain Outcomes.”⁸³⁶

413. At the same time, however, Janssen’s launch plans show it planned to market Nucynta IR as a way to *prevent* acute pain from becoming chronic pain. The Market Overview Strategic Plan included “Elevate the concept of early, effective acute pain management to limit

⁸³⁴ JAN-MS-00350627 at slide 40 (emphasis added).

⁸³⁵ JAN00012142 at 33.

⁸³⁶ JAN-MS-00457581 at 9.

pain progression” and “Potentially reduce the risk for the development of chronic pain” as objectives.⁸³⁷

(b) Disrupting the Complacent Market

414. Early on, Janssen identified “complacent” or “habitual” prescribing as a hurdle to Nucynta’s success, and its launch materials speak of the need to “disrupt” this status quo.

414.1. In its 2008 Tapentadol Business Plan, Janssen identified “Habitual market fraught with skepticism” as a “Lesson learned,” as to which the “Action to be taken” was “Establish receptivity to a NME [new molecule].” Another “Lesson learned” listed on the same slide was “Need to disrupt the marketplace in order to accelerate Tapentadol’s uptake,” with the “Action to be taken” “Integrate aggressive pre-marketing un-branded messages.”⁸³⁸

414.2. The same Business Plan noted that there was a “Habitual market dominated by generics” and that Janssen’s strategy for market entry should “balance the ability to break habitual prescribing vs. the risk of ‘niching’.”⁸³⁹

414.3. Similarly, Janssen’s 2009 Tapentadol Business Plan noted that there was a “Generic dominant, habitual and satisfied/complacent market” among prescribers.⁸⁴⁰ The first “Market Entry Approach” for Nucynta IR and ER listed in this Business Plan was “Successful unbranded campaign to disrupt the market place through flawless field launch readiness.”⁸⁴¹

⁸³⁷ *Id.* at 31.

⁸³⁸ JAN-MS-00443233 at 2.

⁸³⁹ *Id.* at 3.

⁸⁴⁰ JAN-MS-00477361 at 12.

⁸⁴¹ *Id.* at 27 (emphasis in original).

414.4. Janssen's 2009 "Market Overview Strategic Plan" likewise referenced a need for/to "Disrupting the Complacent Marketplace," "Disrupt the habitual generic marketplace" and "disrupt the market place in the unbranded followed by branded phases."⁸⁴² It also answered the strategy question of "What do we need to do?" with "Disrupt the satisfied marketplace."⁸⁴³

414.5. The same Strategic Plan identified "Habitual and Seemingly Satisfied Prescribing" as a "Key Challenge for Entering the CII Opioid Market," and "Satisfied, habitual prescribing by physicians" as a "Market Entry Hurdle" calling for disruption."⁸⁴⁴

414.6. A 2010 Nucynta Business Plan also identified "Habitual and Seemingly satisfied marketplace" as a challenge, and listed on a slide regarding "payer feedback" "**Largely satisfied market** (low level of perceived unmet need)."⁸⁴⁵

(c) Pre-Market FDA Statements Regarding the Safety and Efficacy of Nucynta IR

415. In the context of the growing abuse crisis, the FDA was concerned about the potential for abuse with Nucynta, as shown by pre-approval communications between Janssen and FDA. FDA also raised concerns about Janssen making unsubstantiated comparative and/or superiority claims comparing Nucynta and oxycodone.

416. In a November 20, 2008 FDA Memorandum re: Labeling Addendum incorporated into FDA's Medical Review(s) of the NDA for Nucynta IR of the same date, FDA stated that its Controlled Substances Staff, in their review of the abuse liability data, "noted that studies with tapentadol had findings consistent with a very high abuse liability (similar to

⁸⁴² JAN-MS-00457581 at 15, 35.

⁸⁴³ *Id.* at 102.

⁸⁴⁴ *Id.* at 6, 128, 152.

⁸⁴⁵ JAN-MS-00350627 at 7, 25 (emphasis in original).

hydromorphone),” and therefore found that “additional patient education is considered prudent and necessary to mitigate abuse.”⁸⁴⁶ FDA stated that a Medication Guide was thus being added to the drug’s labeling.

417. In the Risk Benefit Analysis summary of the Medical Office Review (“MOR”) of Nucynta IR, FDA’s Clinical Team Leader Dr. Ellen W. Fields found that Nucynta IR had “a safety profile very similar to that of other immediate release opioid analgesics and tramadol” and that “The risk/benefit analysis for tapentadol IR [wa]s similar to that of other opioid analgesics and Tramadol.”⁸⁴⁷

418. Dr. Fields further observed in the Risk Benefit Analysis that in a Phase 1 study, tapentadol was found to have an abuse liability similar to hydromorphone. She also noted that when subjects in a Phase 3 study abruptly discontinued tapentadol, 17% experienced at least one withdrawal symptom.⁸⁴⁸

419. In a discussion of this Phase 3 study later in the MOR, it is noted that the percentage of subjects with objective signs of withdrawal using the Clinical Opiate Withdrawal Scale (COWS) was 17% in the tapentadol group and 29% in the oxycodone group.⁸⁴⁹ It is also noted, however, that using the Subjective Opiate Withdrawal Scale (SOWS), there was no

⁸⁴⁶ Center for Drug Evaluation and Research, APPLICATION NUMBER:22-304, MEDICAL REVIEW(S), Part 1, at 3. available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_MedR_P1.pdf (last visited March 20, 2019), FDA Memorandum re: Labeling Addendum dated November 20, 2008, part of FDA’s Medical Review(s) of Tapentadol of the same date

⁸⁴⁷ Center for Drug Evaluation and Research, APPLICATION NUMBER:22-304, MEDICAL REVIEW(S), Part 1. at 9. available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_MedR_P1.pdf (last visited March 20, 2019), FDA Medical Officer Review for Tapentadol, January 23, 2008

⁸⁴⁸ *Id.*

⁸⁴⁹ Center for Drug Evaluation and Research, APPLICATION NUMBER:22-304, MEDICAL REVIEW(S), Part 2. at 71, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_MedR_P2.pdf (last visited March 20, 2019), FDA Medical Officer Review for Tapentadol, January 23, 2008, at 153.

statistically significant difference in the withdrawal severity between the two groups, and the same percentage in the two groups experienced drug withdrawal syndrome.⁸⁵⁰

420. The MOR included under “Recommendations for Postmarketing Risk Management Activities” a “Tapentadol IR Safety Surveillance Plan” Janssen had submitted on FDA’s request,⁸⁵¹ in which Janssen listed “potential for abuse” as an “important identified risk,” and “potential for...patient misuse” and “diversion” as “important potential risks.”⁸⁵²

421. Janssen also asked FDA whether it could make comparator/superiority claims for Nucynta in its labeling and marketing as early as 2003. FDA’s minutes from a November 13, 2003 “Type C Industry Meeting” with Janssen regarding development of the compound state:

The sponsor asked whether they may list the AEs of active comparators. Dr. Hertz said that this would not be allowed. Comparative claims carry a high burden of proof and must be replicated. Any mention of comparative data will be removed completely from the label unless there is an adequate body of evidence to justify its inclusion....The sponsor asked about the policy on comparative data as it relates to promotional material. Dr. Hertz said that that would need to be evaluated by the Division of Drug Marketing and Communication (DDMAC). Dr. Permutt clarified that a replicated head-to-head comparison of study drug with a comparator would be required to obtain a superiority claim.⁸⁵³

422. FDA reinforced this point over three years later when Janssen again raised making comparator or superiority claims at a pre-approval meeting with the FDA on June 5, 2007. The FDA’s meeting minutes indicate that Janssen sought to include on the Nucynta IR label a non-inferiority analysis comparing the potency of Nucynta to oxycodone. Dr. Hertz of

⁸⁵⁰ *Id.* at 72.

⁸⁵¹ JAN-0004-0013922 (“We also note the draft proposal does not include detailed information about surveillance and intervention components to monitor for appropriate use and abuse, which are important elements of many of the current risk management programs for opioids. Please remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal.”) *Id.* at 16.

⁸⁵² Center for Drug Evaluation and Research, APPLICATION NUMBER:22-304, MEDICAL REVIEW(S), Part 1. at 9-10. available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_MedR_P1.pdf (last visited March 20, 2019), FDA Medical Officer Review for Tapentadol, January 23, 2008.

⁸⁵³ JAN-MS-01031602 at 6.

FDA “responded that this type of information would not be considered appropriate for inclusion in the label.”⁸⁵⁴

(d) Pre-Market FDA Statements Regarding the Safety and Efficacy of Nucynta ER

423. FDA also raised concerns regarding the potential for abuse and dependence of Nucynta ER prior to its approval. In a September 9, 2010 Memorandum to Dr. Bob Rappaport, FDA’s Director of the Division of Anesthesia and Analgesia Products (“DAAP”), from Dr. Alicja Lerner, a Medical Officer with FDA’s Controlled Substance Staff, concerning Nucynta ER, Dr. Lerner stated, “This is our response to the DAAP consult regarding the abuse related safety issues, including overdose, withdrawal, misuse and abuse of Nucynta ER (Tapentadol ER).”⁸⁵⁵ Dr. Lerner concluded that:

423.1. “The controlled release properties of the TRF [tamper resistant formulation] formulation can be readily overcome by multiple simple physiochemical manipulations.”^{856 857}

423.2. “The to be marketed formulation [also referred to as TRF] exhibits an increased frequency of abuse related adverse events.”⁸⁵⁸

423.3. “In a Phase 1 study in healthy subjects (R331333-PAI-1028), 50% of the [TRF] subjects exhibited euphoria at 250mg.”⁸⁵⁹

⁸⁵⁴ JAN-0004-0013922 at 9.

⁸⁵⁵ Center for Drug Evaluation and Research, APPLICATION NUMBER: 200533Orig1s000, OTHER REVIEW(S), at 70-74, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000OtherR.pdf (last visited March 20, 2019), Letter from Dr. Nelson to Dr. Rappaport dated September 9, 2010.

⁸⁵⁶ *Id.* at 71.

⁸⁵⁷ What was referred to as the “TRF” formulation in the NDA was what was approved and marketed as Nucynta ER.

⁸⁵⁸ *Id.* at 72.

423.4. “In the pooled AE analysis Phase 1 single-dose studies, 5.5% of [TRF] subjects exhibited euphoria, and 8.1% of subjects reported ‘feeling drunk’ as compared to 1% and 0% subjects taking other ER formulations, respectively.”⁸⁶⁰

423.5. “Further, withdrawal symptoms, including insomnia, depressed mood, depression, suicidal ideation, and disturbance in attention, occurred after Tapentadol ER was stopped. Such withdrawal symptoms are common to all mu agonist opioids.”⁸⁶¹

424. Dr. Lerner’s recommendations based on these conclusions included:

424.1. “Because the drug product at the 250 mg dose level appears to result in a high percentage of euphoria and other Opioid like adverse events, the sponsor must provide an adequate rationale for marketing the dose, so that the benefits continue to outweigh the risks.”⁸⁶²

424.2. “Upon approval and marketing, the drug product should continue to be monitored for abuse, misuse, overdose, and withdrawal.”⁸⁶³

425. A July 12, 2011 Memorandum from Dr. Lerner to Dr. Rappaport concerning Nucynta ER reiterated the conclusions in the September 2010 memo, and also noted that “the TRF formulation, in particular the dose of >150mg, appears to exhibit an increased frequency of adverse events (e.g. euphoria) signaling abuse potential.”⁸⁶⁴

⁸⁵⁹ *Id.* at 72.

⁸⁶⁰ *Id.* at 72.

⁸⁶¹ *Id.* at 72.

⁸⁶² *Id.* at 72.

⁸⁶³ *Id.* at 73.

⁸⁶⁴ Center for Drug Evaluation and Research, APPLICATION NUMBER: 200533Orig1s000, OTHER REVIEW(S), at 38-42, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000OtherR.pdf (last visited March 20, 2019), July 12, 2011 letter from Dr. Lerner to Dr. Rappaport.

426. Dr. Lerner's conclusions and recommendations were included in the Medical Review(s) for Nucynta ER dated July 29, 2011.⁸⁶⁵ However, in a subsequent August 3, 2011 letter from the Director of FDA's Controlled Substances Staff, Dr. Michael Klein, to Dr. Rappaport, Dr. Klein withdrew Dr. Lerner's recommendations and conclusions from the September 9, 2010 memo following a meeting with the Controlled Substances Staff and Office of Clinical Pharmacology (OCP).⁸⁶⁶ Dr. Klein found that Dr. Lerner's adverse event analysis "covered a limited area of investigation," and that her conclusions "are insufficient to override the analyses and conclusions of the reviewer of the full range of clinical studies."

427. Left unchanged by the August 3, 2011 memo was the Summary Review for Regulatory Action included in the Medical Review(s), dated October 1, 2010, which stated that, "With respect to specific safety concerns, such as abuse potential, dependence, withdrawal and neuropsychiatric adverse events, the safety profile of extended-release tapentadol appeared to be consistent with other products with similar pharmacologic properties. There is suggestion that extended-release tapentadol may have abuse potential and dependence/withdrawal characteristics similar to long acting opioids."⁸⁶⁷

428. Janssen sought FDA's authorization to include a Tamper Resistant Formula (TRF) claim on the Nucynta ER label, but FDA did not permit the labeling claim. Upon review of the

⁸⁶⁵ Center for Drug Evaluation and Research, APPLICATION NUMBER: 200533Orig1s000, MEDICAL REVIEW(S), at 8-9, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000MedR.pdf (last visited March 20, 2019), FDA Medical Review(s) for Nucynta ER, July 29, 2011.

⁸⁶⁶ Center for Drug Evaluation and Research, APPLICATION NUMBER: 200533Orig1s000, OTHER REVIEW(S), at 12-14, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000OtherR.pdf (last visited March 20, 2019), August 3, 2011 letter from Dr. Klein to Dr. Rappaport.

⁸⁶⁷ Center for Drug Evaluation and Research, APPLICATION NUMBER: 200533Orig1s000, MEDICAL REVIEW(S), at 67, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000MedR.pdf (last visited March 20, 2019), FDA Summary Review for Regulatory Action, October 1, 2010, at page 12.

TRF data Janssen provided, FDA found that the data “shows that none of these studies are robust and compelling enough to support abuse-deterrent Tier 1, 2, or 3 labeling claims for various routes of administration.”⁸⁶⁸

429. When Janssen invoked the “low rate of abuse” in the postmarketing data for Nucynta IR and ER in support of its request for TRF labeling, FDA responded:

The low rate of abuse of both tapentadol IR and ER in the community is promising, *but the data do not yet provide sufficient evidence to confer a Tier 4 claim for Nucynta ER. At this point in time, it is unclear whether the relatively low amount of abuse detected is due to a low level of awareness of the drug as a consequence of its short marketing history, low utilization, reduced opioid receptor affinity of the tapentadol molecule, or the tamper resistant characteristics of the extended-release formulation.* Due to the lack of a non-abuse-deterrent comparator, detecting meaningful change in the level of community abuse is challenging. You have chosen adequate data sources to depict the current extent of abuse in the community, but *the limited time frame each data source portrays is insufficient to characterize the abuse profile of Nucynta ER.* To determine if the current trend remains stable over time, continued surveillance and monitoring of Nucynta ER is necessary. The amount of data needed to determine if a trend is stable varies by situation, and the low utilization level for Nucynta ER may extend that time period. Additionally, *the data must be able to show that the smaller amount of abuse in the community is contingent on the drug formulation, and not due to its low utilization or to innate properties of the molecule itself.*⁸⁶⁹

430. I have not located in the record a submission by Janssen of additional data of the type FDA requested, and the Nucynta ER label was never changed to include a TRF claim.

2. Janssen’s Marketing of Nucynta Overstated its Benefits.

431. Janssen’s marketing adopted “powerful efficacy with unprecedented tolerability” as the key promotional tagline for “disrupting” the “complacent” or “satisfied” opioid market.⁸⁷⁰ Three primary messages of this approach were 1) a unique dual mechanism of action that would

⁸⁶⁸ FDA Preliminary Meeting Comments, August 5, 2013, JAN-MS-02043301 at 3.

⁸⁶⁹ JAN-MS-02043301 at 6-7 (emphasis added) , FDA Preliminary Meeting Comments, August 5, 2013.

⁸⁷⁰ JAN-MS-00477361 at 24; JAN-MS-00457581 at 89; JAN00012142 at 8.

increase efficacy; 2) fewer gastrointestinal (“GI”) side effects; and 3) less abuse liability and withdrawal.

432. These were the first three “Key attributes perceived to differentiate [Nucynta] from existing chronic pain medications” identified in an August 2010 Nucynta ER Payer and Physician Research PowerPoint: “Increased tolerability due to lower GI side effects;” “Decreased abuse potential and tamper-resistant properties;” “Dual mechanism of action.”⁸⁷¹

433. These messages were used to differentiate Nucynta from other analgesics, particularly OxyContin/oxycodone. In my opinion, these superiority claims were neither contained in the label nor supported by substantial evidence, and overstated Nucynta’s benefits while understating its risks.

(a) Janssen Overstated the Benefits of Nucynta’s Mechanism of Action

434. The Nucynta IR and ER labels have stated from the beginning that tapentadol’s exact mechanism is unknown. Through 2010, the IR label additionally stated that “its effect is thought to be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake.”⁸⁷² As of 2013, this language changed to “Although the clinical relevance is unclear, preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI). Analgesia in animal models is derived from both of these properties.”⁸⁷³ The latter language has been the language used in the Nucynta ER label since approval.

⁸⁷¹ JAN-MS-00473858 at 36

⁸⁷² Nucynta IR label, 2008, JAN-MS-00445032; Nucynta IR label, 2009, JAN-MS-01249732; Nucynta IR label, 2010, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022304s0031bl.pdf (last visited March 20, 2019)

⁸⁷³ Nucynta IR label, July 2013, JAN-MS-01229368; Nucynta IR label, October 2013, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022304s014s0151bl.pdf (last visited March 20, 2019); Nucynta IR label, December 2016, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022304s0161bl.pdf (last visited March 20, 2019);

435. Prior to launching Nucynta, Janssen identified its purported “unique dual mechanism of action” as a primary means to differentiate the drug from competitors and “disrupt” habitual prescribing. Janssen’s launch materials indicated it planned to use this message to suggest that Nucynta had unique efficacy in “mixed” pain, and that it reduced the need for patients to take additional opioids (a characteristic referred to by Janssen as “opioid sparing”).

435.1. Janssen’s 2008 Tapentadol Business Plan noted that a “Key IR Message” and “Value Proposition” for Nucynta IR was that it was a “Centrally acting analgesic with dual mechanism of action.”⁸⁷⁴

435.2. The same 2008 Business Plan stated on a slide entitled “Phase IV Clinical Development Strategies” “Bridge the gap between pre-clinical and clinical perspective regarding MOA--Demonstrate versatility of the molecule in PCP- relevant pain models.” The slide suggested that the “Dual MoA” led to greater efficacy and safety.⁸⁷⁵

435.3. The 2008 Business Plan further stated on a “Brand Vision” slide that the dual MOA had “‘Opioid Sparing’ Effects” which would mean less withdrawal symptoms and less dose escalation.⁸⁷⁶ No evidence was cited for these claims.

Nucynta IR label, September 2018, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022304s019s0211bl.pdf (last visited March 20,2019); Nucynta ER label, 2011, JAN-MS-02544901; Nucynta ER label, July 2012, JAN-MS-00229587; Nucynta ER label, August 2012, JAN-MS-00229558; Nucynta ER label, April 2014, JAN-MS-03088328; Nucynta ER label, December 2016, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/200533s0141bl.pdf (last visited March 20,2019); Nucynta ER label, September 2018, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/200533s018s0191bl.pdf (last visited March 20,2019).

⁸⁷⁴ JAN-MS-00443233 at 10.

⁸⁷⁵ *Id.* at 11.

⁸⁷⁶ *Id.* at 12.

435.4. A September 2008 press release Janssen drafted in anticipation of Nucynta IR's approval stated "Nucynta has a unique profile with two mechanisms of action, combining mu-opioid receptor agonism and norepinephrine reuptake inhibition in a single molecule."⁸⁷⁷ In a September, 2008 email chain addressing the draft, Janssen executive Kathleen Dusek stated that based on a review of an FDA warning letter, the word "unique" (among others in the press release) "might be contentious," and went on to assert "We do not have clinical data to support the dual mechanism of action. Generally, FDA feels that preclinical evidence is not enough."⁸⁷⁸ The language Dusek identified was removed from the final version of the press release, but the company continued to tout the the benefits of Nucynta's dual MoA in its promotional materials, as noted below.

435.5. In a SWOT analysis in its 2009 Tapentadol Business Plan, Janssen listed among Nucynta's strengths "Dual Mechanism of Actions in 1 molecule," but then listed among its weaknesses "Norepinephrine benefit not clear/quantifiable."⁸⁷⁹

435.6. In its 2009 "Marketing Overview Strategic Plan," Janssen again stated that the drug's "Dual MOA-Opioid Sparing Effects" was a "Value Proposition" that would lead to "less withdrawal symptoms," "less dose escalation (durability)," and "emotional wellbeing."⁸⁸⁰ No evidence was cited for these claims.

⁸⁷⁷ JAN-MS-01124875 at 2-4.

⁸⁷⁸ JAN-MS-01124875.

⁸⁷⁹ JAN-MS-00477361 at 19, 20.

⁸⁸⁰ JAN-MS-00457581 at slide 10.

435.7. Another slide in the 2009 Plan stated “The μ -opioid-sparing effect message should be emphasized (opiophobia is common in primary care).”⁸⁸¹

435.8. In a slide in the same 2009 Plan on “Optimizing Analgesic Therapy for Moderate to Severe Pain,” Janssen listed an objective of “Highlight recent research supporting the benefits of multi-modal therapy to maximize analgesic efficacy and minimize side effects” in order to “Set the stage for introduction of tapentadol,” “An agent with mu-opioid agonist and NE-reuptake inhibition mechanisms of analgesia.”⁸⁸² No such research was cited.

435.9. In slides in the same 2009 Plan regarding speaker and KOL engagements, unbranded publications, and secondary publications, Janssen’s notes to the slides stated these would “Support the rationale for an agent with two MOAs.”⁸⁸³

435.10. A “Tested Positioning Statement” in the 2009 Plan presented a “The Best of Both Worlds” statement. This statement asserted that Nucynta provided “pain relief without tradeoffs,” which was unsupported by substantial evidence:

Product X [Nucynta] is the only *dual-acting*, single-agent, Schedule II analgesic linking powerful opioid efficacy with unprecedented tolerability that enables physicians to provide *pain relief without tradeoffs* because it *selectively works on both the mu-opioid and norepinephrine pathways for optimal pain control* without treatment-compromising side effects.⁸⁸⁴

435.11. An “APS [American Pain Society] Activities” section of the 2009 Plan indicated that Janssen would be sponsoring an APS booth that would feature several

⁸⁸¹ *Id.* at 41.

⁸⁸² *Id.* at 33.

⁸⁸³ *Id.* at 35, 49, 153.

⁸⁸⁴ *Id.* at 89 (emphasis added).

Janssen posters, including one called “Pathways,” which stated “Multimodal pathways that address more than one pathway may provide more comprehensive relief.”⁸⁸⁵

435.12. Janssen’s 2010 Nucynta Business Plan identified as a “lever of growth” “Drive the **mixed / multi-etiology of pain consideration for a broader pain types using the dual MOA followed by DPN findings as the proof of concept and** rational [sic] for first line / foundation of management.”⁸⁸⁶

435.13. Two slides later, however, the 2010 Business Plan recognized as a “challenge” the fact that “MOA is a proof of concept only.”⁸⁸⁷

435.14. Similarly, a slide in the 2010 Plan listing “Strengths” notes “Dual MOA resonates with mu-receptor sparing effects,” but the next slide on “Weaknesses” noted “Norepinephrine benefit not clear/quantifiable.”⁸⁸⁸

435.15. Janssen’s 2011 Nucynta ER Launch Plan identified “Unique Mechanism of Action” as a “Nucynta ER Core Message,” and asserted that “Unlike traditional opioids, Nucynta has 2 proven analgesic mechanisms.”⁸⁸⁹

435.16. The 2011 ER Launch Plan also indicated that in a presentation on osteoarthritis data for Nucynta, physicians identified the key message as “A new pain medication with equal or greater efficacy than OxyContin, but fewer side effects, less discontinuation and a dual MOA.”⁸⁹⁰

⁸⁸⁵ *Id.* at 54, 65.

⁸⁸⁶ JAN-MS-00350627 at 5. (Emphasis in original.)

⁸⁸⁷ JAN-MS-00350627 at 7.

⁸⁸⁸ JAN-MS-00350627 at 10, 11.

⁸⁸⁹ JAN00012142 at 8.

⁸⁹⁰ *Id.* at 22.

435.17. A slide entitled “Tapentadol answers the unmet need” in the 2011 Launch Plan contained the position statement that Nucynta is “the only broad coverage analgesic that provides superior outcomes” because... “Dual MOA, (MU/NRI) provide opioid-sparing benefits.”⁸⁹¹

436. Once Nucynta was on the market, Janssen continued to promote the purported “unique dual mechanism of action” of Nucynta as a primary means to differentiate the drug from competitors and “disrupt” habitual prescribing. Janssen’s marketing materials falsely suggested that this mechanism imparted to Nucynta unique efficacy in certain types of pain, particularly back and neck pain, and reduced the need for patients to take additional opioids.

436.1. A May 2010 recap of a “Nucynta Ask the Expert Call” for sales representatives shows that in response to a discussion of the norepinephrine mechanism, Janssen suggested that the representatives “d[idn’t] need to get into the science” but should ask, “Why would you not use a drug that hits pain from multiple pathways?”⁸⁹² In the Nucynta FAQ (Frequently Asked Questions) referred to in the recap, the response to the FAQ of “What is the contribution of analgesia of NUCYNTA through mu-receptor agonism and norepinephrine reuptake inhibition?” is “This is currently being investigated by Grunenthal and at this point we cannot comment.”⁸⁹³

436.2. In Janssen’s 2012 Nucynta and Nucynta ER Business Plan, Janssen laid out a marketing strategy to “generate data to support MoA differentiation” in order to “strengthen differentiation and value through new & compelling evidence.”⁸⁹⁴

⁸⁹¹ *Id.* at 30.

⁸⁹² JAN-MS-03007471; JAN-MS-03007472

⁸⁹³ JAN-MS-03024758; JAN-MS-03024760.

⁸⁹⁴ JAN-MS-00010801 at 12, 42.

436.3. A SWOT analysis in the 2012 Business Plan identified among the drug's strengths "New molecular entity (dual MOA)," and among its opportunities "MOA & GI Tolerability benefits more meaningful in chronic pain."⁸⁹⁵

436.4. A "Pain Business Review" for Nucynta IR & ER dated April 23, 2014 contained a "NUCYNTA ER Positioning Statement" asserting that Nucynta "offers a superior overall clinical profile **because:** it provides best-in-class efficacy across multiple pain types... and a unique dual MOA **so that:** physicians and patients can achieve their individualized pain improvement goals without many of the challenges typically associated with traditional opioids."⁸⁹⁶ No evidence was cited to support these claims.

436.5. The Review identified among the "RTBs [reasons to believe]" for the Positioning Statement the following: "Dual MOA with mu-opioid agonism and norepinephrine reuptake inhibition."⁸⁹⁷

437. In his deposition, Janssen's former Director of Sales and Marketing, David Lin, testified that the dual mechanism was based solely upon pre-clinical animal studies.⁸⁹⁸ He also agreed that "if the exact mechanism of action is unknown, that renders it difficult, if not impossible, to unequivocally make statements about dual mechanism of action."⁸⁹⁹

438. Janssen's sales call notes show that its sales representatives nonetheless frequently promoted Nucynta's "unique" "dual" mechanism of action to healthcare providers,

⁸⁹⁵ *Id.* at 61.

⁸⁹⁶ JAN-MS-02389698 at 73 (emphasis in original).

⁸⁹⁷ *Id.* at 74.

⁸⁹⁸ David Lin Dep., 91:12 -95:4 (December 20, 2018).

⁸⁹⁹ David Lin Dep., 74:5 -79:12 (December 20, 2018).

without the qualification on the label that the exact mechanism is unknown. The large majority of call notes for Nucynta make these unsupported claims. For example:

438.1. One Illinois call note from July 2009 reports, “I was able to speak with dr Chami about the advantages of having the dual MOA and he told me that he can see how Nucynta would benefit his patients. He also felt that this could keep him from having to use two pain meds for treatment of the back and neck pain patient.”⁹⁰⁰

438.2. Another Illinois call note from that same month described speaking “with the dr about the fact that Nucynta Dual MOA and what advantages Nucynta will provide patients that suffer from Back and neck pain.”⁹⁰¹

438.3. A Wisconsin call note from August 2009 states that the sales representative “discussed Nucynta's dual moa and how it could help provide more of a comprehensive approach to pain management, along with comparable efficacy to oxy ir as well as an excellent safety profile makes Nucynta an ideal treatment option to pts with acute pain askd her what her hesitation was in trialing Nucynta, she indicated its newness.”⁹⁰²

438.4. From 2013 to 2015, “MOA” or “Mechanism of action – Nucynta ER” was listed as the message for 89 sales calls or visits for Nucynta ER.⁹⁰³

439. In my opinion, Janssen overstated the benefits of Nucynta’s mechanism of action, promoting it as offering increased efficacy and fewer side effects without substantial evidence.

⁹⁰⁰ JAN00118971. Additional call notes can be found in Schedule 11.

⁹⁰¹ *Id.*

⁹⁰² *Id.*

⁹⁰³ JAN00118960.

(b) Janssen Overstated the Benefits of Nucynta's GI Tolerability

440. Prior to launching Nucynta, Janssen identified the drug's purportedly superior GI tolerability as another principal means of differentiating the drug from competitors and "disrupting" "satisfied" prescribing. Janssen's launch materials indicated it planned to highlight this message from the outset.

440.1. In one of its earliest launch plans for Nucynta, Janssen identified "Improved GI Tolerability (Nausea & Vomiting)" as a "Key product attribute."⁹⁰⁴

440.2. In its 2008 Tapentadol Business Plan, Janssen identified "Integrate aggressive pre-marketing un-branded messages--Unmet need (GI, CNS)" as an "Action to be taken" "to disrupt the marketplace" and "accelerate Tapentadol's uptake."⁹⁰⁵

440.3. In the 2008 Plan Janssen also identified "Amplify tolerability (GI; CNS) with additional safety markers" as an "execution driver" for the "brand strategy" of "Establishing a differentiated and customer-compelling value proposition to get most favorable formulary access."⁹⁰⁶

440.4. The 2008 Business Plan also noted that a "Key IR Message" and "Value Proposition" for Nucynta IR was "*GI Tolerability superior to oxycodone* at comparable doses (NI Study)"⁹⁰⁷ (emphasis added).

440.5. Janssen's 2009 Business Plan for Nucynta asserted that Nucynta had "Typical opioid-related AEs, but, compared with oxycodone at equipotent doses: Less constipation; Less nausea – **superiority claim at launch**; Less vomiting - **superiority**

⁹⁰⁴ JAN-MS-01053692 at slide 15.

⁹⁰⁵ JAN-MS-00443233 at slide 2.

⁹⁰⁶ *Id.* at 4.

⁹⁰⁷ *Id.* at 10 (emphasis added).

claim at launch” (bold emphasis added).⁹⁰⁸ The support cited for these claims consisted of tolerability studies lasting 3 to 90 days.

440.6. The 2009 Business Plan identified as a “Market Entry Approach” for Nucynta IR and ER “Timely completion of differentiation studies including the bunionectomy additional end-stage OA to support superiority claims in GI side effects.”⁹⁰⁹

440.7. In a “Tapentadol Value Propositions” slide in Janssen’s 2009 “Marketing Overview Strategic Plan,” the drug’s “Lower side effect (GI and pruritis)” was cited in support of the value proposition of “Comprehensive Efficacy with Superior tolerability.”⁹¹⁰ No evidence was provided for the lower side effect claims, which did not appear on the drug’s label.

440.8. A slide from the 2009 Plan entitled “Current Treatment Dynamics” showed “Opioid induced GI side effects” leading to “Inadequate management of acute pain,” for which tapentadol would be a solution.⁹¹¹

440.9. An “APS [American Pain Society] Activities” section of the 2009 Plan indicated that Janssen would be sponsoring an APS booth that would feature several Janssen posters, including one regarding side effects, which characterized patients’ “concerns about opioid related GI side effects” as a “barrier that leads to undertreatment of moderate to severe pain.”⁹¹²

⁹⁰⁸ JAN-MS-00477361 at 5 (emphasis added).

⁹⁰⁹ *Id.* at 27 (emphasis in original).

⁹¹⁰ JAN-MS-00457581 at 10.

⁹¹¹ *Id.* at 12.

⁹¹² *Id.* at 54, 65.

440.10. In the same Strategic Plan, Janssen instructed “Highlight the importance of side effects (especially constipation) as a culprit for achieving optimal management” as a “Seed of disruption” to address the “Market Entry Hurdle” of “Lack of patient-physician dialogue to surface patient dissatisfaction.”⁹¹³

440.11. The Strategic Plan also highlighted the value of marketing “Reduction of GI AEs” to pharmacists, recommending messages of “Reduced need for laxatives and other concomitant meds,” and “Shorter duration of GI AEs may improve compliance and overall QOL.”⁹¹⁴

440.12. “Offers GI tolerability that is superior to oxycodone in both opioid-naïve and opioid-experienced patients” and “Provides superior tolerability with a 50% reduction in GI-induced side effects vs. Oxycodone IR” are identified as “Brand Lifting” statements that are among the “Key Features to Keep in Messaging” in two different slides in the Strategic Plan.⁹¹⁵

440.13. A September 2008 press release Janssen drafted in anticipation of Nucynta IR’s approval stated, “The studies also showed that treatment with [Nucynta] for acute moderate to severe pain is associated with a favorable gastrointestinal side effect profile, compared to oxycodone, a commonly used prescription medication for moderate to severe pain.”⁹¹⁶ In a September 2008 email chain addressing the draft, Janssen executive Kathleen Dusek stated that “While we might be able to say ‘potential for a favorable GI side effect profile,’ ...the data in the NOA do not really support saying we

⁹¹³ *Id.* at 6, 128, 152 (emphasis in original).

⁹¹⁴ *Id.* at 45.

⁹¹⁵ *Id.* at 90, 92.

⁹¹⁶ JAN-MS-01124875 at 2-3.

have a favorable GI profile *against oxy.*”⁹¹⁷ The language Dusek identified was removed from the final version of the press release, but the company continued to tout Nucynta’s “better” GI tolerability in its promotional materials, as noted below.

440.14. A 2010 Nucynta Business Plan noted that while there was a “**Largely satisfied market** (low level of perceived unmet need),” “Physicians and patients identify AEs (particularly GI) as key areas of unmet need.”⁹¹⁸

440.15. Janssen’s 2011 Nucynta ER Launch Plan identifies “Better GI Tolerability” as a “Nucynta ER Core Message,” and beside it notes that “Fewer discontinuations means more patients can achieve pain relief.”⁹¹⁹

441. After launch, Janssen continued to promote the purported greater gastrointestinal tolerability of Nucynta as a key tool in differentiating the drug from competitors and “disrupting” “complacent” prescribing. Janssen’s marketing materials falsely suggested that Nucynta had demonstrated superiority over competitor drugs with regards to GI tolerability.

441.1. A SWOT analysis in Janssen’s 2012 Nucynta and Nucynta ER Business Plan identified among the drug’s strengths “Robust clinical data - proven efficacy vs std of care, better GI tolerability, (IR, ER),” and among its opportunities “MOA & GI Tolerability benefits more meaningful in chronic pain.”⁹²⁰

441.2. A “Video Walk –Through” sales aid and script dated June 6, 2012, contained a screen shot with a header stating “Make NUCYNTA ER Your Choice for Chronic Pain” along with tabs including “Dual Mechanism of Action,” “Efficacy,” and

⁹¹⁷ JAN-MS-01124875 (emphasis in original).

⁹¹⁸ JAN-MS-00350627 at 7, 25 (emphasis in original).

⁹¹⁹ JAN00012142 at 8.

⁹²⁰ JAN-MS-00010801 at 61.

“Tolerability/Safety/Withdrawal.” Notes underneath the screen shot state, “The low back pain study efficacy, the GI tolerability, and the withdrawal information continue to be the crux of the NUCYTNA ER story, and you should keep reinforcing these critical messages.”⁹²¹

441.3. A “Pain Business Review” for Nucynta IR & ER dated April 23, 2014 contained a “NUCYNTA ER Positioning Statement” asserting that Nucynta “offers a superior overall clinical profile **because:** it provides best-in-class efficacy across multiple pain types... [and] proven GI tolerability **so that:** physicians and patients can achieve their individualized pain improvement goals without many of the challenges typically associated with traditional opioids.”⁹²² No evidence was cited to support these claims.

441.4. The Review identified among the “RTBs [reasons to believe]” for the Positioning Statement the following: “Proven GI tolerability.”⁹²³

441.5. Several Janssen advertisements for Nucynta promoted its “unexpected tolerability” or “tolerability you want” with graphs showing GI tolerability data from clinical studies.⁹²⁴

442. On August 26, 2011, FDA’s DDMAC wrote to Janssen regarding oral statements made by a Janssen representative about Nucynta at a meeting of the American Society of Health-System Pharmacists, which FDA found to constitute unsubstantiated superiority claims and minimization of risk.⁹²⁵

⁹²¹ JAN-MS-00774016 at 6.

⁹²² JAN-MS-02389698 at 73 (emphasis in original).

⁹²³ *Id.* at 74.

⁹²⁴ JAN-MS-00236322 at 2; JAN-MS-00229217 at 5.

⁹²⁵ JAN-MS-02273742.

442.1. DDMAC reported that its representative observed the Janssen representative state at the meeting that “DPNP patients stay on Nucynta for longer, and Nucynta provides 10 mg of opioid/oxycodone pain control, similar to tramadol, but with less GI, constipation, nausea and vomiting.”⁹²⁶

442.2. DDMAC found that this statement “misleadingly implie[d] that Nucynta is clinically superior (i.e., safer) compared to oxycodone and tramadol for DPNP patients. Specifically, it implies that Nucynta has been shown to have less GI adverse reactions (i.e., constipation, nausea, and vomiting)...when this is not the case.”

442.3. FDA noted in the letter that when it reviewed the data from clinical studies for Nucynta involving subjects taking Nucynta and oxycodone, it “determined that the studies were not adequately powered for the analysis of multiple safety endpoints, and that the dose of oxycodone used as a comparator was not demonstrated to be equianalgesic to the doses of Nucynta studies. Therefore, safety comparative data were not considered clinically meaningful and were not included in the approved PII for Nucynta.”⁹²⁷

442.4. FDA further stated that “the sales representative’s claim that Nucynta results in less constipation, nausea and vomiting minimizes the risks associated with the use of Nucynta and suggests that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.”⁹²⁸

442.5. FDA noted that the most common adverse events associated with Nucynta in clinical studies included nausea and vomiting, “and these were also among the most

⁹²⁶ *Id.* at 2.

⁹²⁷ *Id.* at 4.

⁹²⁸ *Id.* at 4.

common reasons for discontinuation of treatment...Additionally, 8 percent of Nucynta-treated patients experienced constipation as an adverse event in clinical studies versus 3 percent in the placebo arm.”⁹²⁹

442.6. FDA requested that Janssen immediately cease its violative promotional activities for Nucynta, and list all “promotional materials for Nucynta that contain violations such as those above.”⁹³⁰

443. Janssen responded that it was “not aware of promotional activities or materials for Nucynta that contain statements/claims such as those described” in FDA’s letter.⁹³¹

444. The materials cited above, however, show that Janssen was in fact engaging in promotional activities containing statements like those described in FDA’s letter, and continued doing so even after its response.

445. In addition, Janssen’s sales call notes show that its sales representatives frequently promoted Nucynta as having lower rates of GI side effects. For example:

445.1. An Ohio call note from June 2009 reported, “The improved GI side effect profile of Nucynta does offer some advantages over some of the other branded IR opioid medications. Unlikely it would be a 2nd tier position, but would be tier 3 for most of Paramount’s plans. Customer was also curious of any evidence of less abuse potential compared to Oxycontin as an example. Significance: Nucynta with its additional GI

⁹²⁹ *Id.* at 4.

⁹³⁰ *Id.* at 4.

⁹³¹ September 12, 2011 letter from Roxanne O. McGregor-Beck, Janssen Associate Director of Regulatory Advertising and Promotion, to Dr. Mathilda K. Fienkeng, Regulatory Review Officer at FDA’s DDMAC. JAN-MS-00230368.

benefits would not likely to be disadvantaged for most plans, and would likely be a tier 3 opioid without restrictions.”⁹³²

445.2. A Wisconsin call note from September 14, 2009 reported, “Talked with Dr Kumar - he said he hasn't used it yet -- he just needs to get comfortable and he has all the information. I told him the only way he is going to get comfortable is to use. Referenced that ... patients are having improvements with tolerability. Pointed out the fact that patients have placebo-like constipation and over 50% less nausea and vomiting. I asked him to identify some patients who are having surgery done and write Nucynta instead of percocet for them so he can be more familiar with it....”⁹³³

445.3. From 2013-2015, there were 8 sales calls/visits for Nucynta ER that had “Proven Tolerability” reported as the key message.⁹³⁴

446. In my opinion, Janssen overstated the benefits of Nucynta’s GI tolerability, making superiority claims without substantial supporting evidence.

3. Janssen’s Promotion of Nucynta Minimized the Risks of Abuse and Withdrawal During an Opioid Abuse Epidemic.

447. Nucynta represented Johnson & Johnson’s and Janssen’s entry into the oral opioids market. At the time Nucynta was first approved at the end of 2008, that market had reached approximately \$7.5 billion in annual sales, with approximately \$2.5 billion in immediate release oral opioids and approximately \$4.6 billion in extended or continuous release oral

⁹³² JAN-OH-00000262. Additional call notes can be found in Schedule 11.

⁹³³ JAN00118971.

⁹³⁴ JAN00118960.

opioids.⁹³⁵ The extended release market was dominated by Purdue's OxyContin, which had \$2.2 billion in sales in 2008.⁹³⁶

448. By the time of Nucynta's approval, there was a growing public health crisis of opioid abuse, particularly of OxyContin/oxycodone, as documented and discussed by many news reports from wide-ranging geographic areas,⁹³⁷ by FDA in Advisory Committee meetings,⁹³⁸ by legal filings,⁹³⁹ and by medical journal articles⁹⁴⁰. As shown below, from early on, Janssen's promotional materials for Nucynta discussed the marketing impact of growing concerns about abuse and turning such concerns to Janssen's advantage. Janssen recognized internally that "increased use is associated with increased abuse and diversion,"⁹⁴¹ but sought to maximize sales of Nucynta while understating the risk of abuse and withdrawal and offering as "solutions" to the abuse problem tools such as its *prescriberesponsibly.com* website,⁹⁴² which minimized the risk of addiction through the concept of "pseudoaddiction."

449. Beginning prior to the approval of Nucynta, Janssen developed marketing plans identifying the medical community's concerns about abuse as a factor in marketing the drug. Those plans sought to allay those concerns, often through understating Nucynta's risk of abuse and withdrawal. At the same time, the plans sought to differentiate Nucynta from

⁹³⁵ Opioid sales totals for 2008 calculated from IQVIA (formerly IMS) data reported in PPLP003364349.

⁹³⁶ *Id.*

⁹³⁷ See PPLPC028000099480; See also PDD8107130029; See also Borger, Juliana. "Hillbilly Heroin: the Painkiller Abuse Wrecking Lives in West Virginia." *The Guardian*, 6 June 2001, available at <https://www.theguardian.com/world/2001/jun/25/usa.julianborger> (last visited March 20, 2019)..

⁹³⁸ See JAN-MS-00616428.

⁹³⁹ See PPLPC018001139508; See also PDD1712900150.

⁹⁴⁰ See PURCHI-000122070; See also PURCHI-000241775; See also JAN-MS-01466935.

⁹⁴¹ JAN-MS-00771526 at 3.

⁹⁴² JAN-MS-00771526 at 31.

OxyContin/oxycodone with regards to abuse liability and withdrawal, even though as noted above FDA had found that Nucynta had a safety profile similar to other opioids.

450. For example, Janssen's pre-launch 2008 Business Plan for Tapentadol contained a "Brand Vision" slide which noted "Less withdrawal symptoms" under "Ease of Management (especially PCPs)." ⁹⁴³

451. Janssen's April 2009 "Market Overview Strategic Plan," dating just prior to the start of sales of Nucynta IR, also identified less withdrawal as a key marketing message.

451.1. A slide asserting that "Under-Management Driven by Side Effects" led to the "Severe Consequences" of acute pain becoming chronic depicted tapentadol as having less withdrawal and "dose creep." ⁹⁴⁴

451.2. "Less withdrawal symptoms" is also identified on a slide entitled "Tapentadol Value Proposition." ⁹⁴⁵

451.3. Another slide identifies "Fewer withdrawal symptoms vs oxycodone upon abrupt discontinuation" among "PCP Relevant Outcomes." ⁹⁴⁶

451.4. In a slide with a "Reasons to Believe" exercise, "Demonstrates fewer and milder withdrawal effects than oxycodone" is identified as a "Brand Lifting" statement that is among the "Key Features to Keep in Messaging." ⁹⁴⁷

451.5. "Withdrawal" is also listed as a factor that is "Critical to [Nucynta] ER formulation VP [Value Proposition]." ⁹⁴⁸

⁹⁴³ JAN-MS-00443233 at 12.

⁹⁴⁴ JAN-MS-00457581 at slide 9.

⁹⁴⁵ JAN-MS-00457581 at 10.

⁹⁴⁶ JAN-MS-00457581 at 41.

⁹⁴⁷ JAN-MS-00457581 at 92.

⁹⁴⁸ JAN-MS-00457581 at 118.

451.6. Nowhere in the slides above is it noted that, as found by FDA in review of Nucynta IR's NDA, lower withdrawal with Nucynta IR was noted using only one opioid withdrawal scale in one study against one comparator opioid (oxycodone), or that another opioid withdrawal scale utilized in the same study did not find meaningfully lower withdrawal compared to oxycodone.⁹⁴⁹ In addition, as noted above, FDA found in its MOR of Nucynta ER that it had dependence/withdrawal characteristics similar to other long acting opioids.⁹⁵⁰ I can find no evidence in the record that Janssen obtained FDA approval to make a superiority claim on the label of Nucynta IR or ER of less withdrawal than oxycodone or any other opioid.

452. Janssen's Tapentadol Global Commercial Team PowerPoint dated April 15, 2009, shortly before sales of Nucynta IR began, included the following slides about addiction concerns:

452.1. A slide on "Current Treatment Dynamics" showing "Fear of Addiction and abuse" leading to "Inadequate management of acute pain," for which Tapentadol would be a solution.⁹⁵¹

452.2. A slide entitled "Opiophobia," showing "Fear of addiction" leading to "Myths" and "Fear of diversion," in turn leading to "Fears preclude patient validation of true pain."⁹⁵²

452.3. A slide entitled "Market Dynamics—Barriers," listing "Fear of addiction" and "Entrenchment of Oxycodone."⁹⁵³

⁹⁴⁹ Center for Drug Evaluation and Research, APPLICATION NUMBER:22-304, MEDICAL REVIEW(S), Part 2. at 71, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_MedR_P2.pdf (last visited March 20, 2019), FDA Medical Officer Review for Tapentadol, January 23, 2008, at 72, 153.

⁹⁵⁰ *Id.*

⁹⁵¹ JAN-MS-00457581 at 12.

⁹⁵² JAN-MS-00457581 at 69.

452.4. A slide entitled “Tapentadol Brand Map,” listing under “Unmet Needs” “Efficacy of oxycodone without the baggage.”⁹⁵⁴

453. Similarly, launch plans for Nucynta ER indicated the importance of concerns about abuse, and the ability to distinguish Nucynta with regards to abuse, to Janssen’s plans to market the drug:

453.1. A 2011 Draft Nucynta Business Plan dated July 27, 2010 asked on a slide entitled “Key Business Questions: Tapentadol ER:” “Can tapentadol ER demonstrate lower abuse potential?”⁹⁵⁵

453.2. Another slide in this 2010 PowerPoint entitled “Strategies & Executional Drivers” listed several comparisons of Nucynta ER to “oxy” under “Strengthen differentiation,” including “reduced abuse potential.”⁹⁵⁶

453.3. A slide regarding “Key Prescriber Insights” on Nucynta noted that a “Driver” for Primary Care was “low perceived addiction and/or abuse potential.”⁹⁵⁷

453.4. A slide listing “2011 Opportunities,” includes “OxyContin fatigue w/payers/Purdue irresponsibility.”⁹⁵⁸

453.5. In a July 21, 2011 “Promotional Platform: Physicians & Payers” PowerPoint addressing the launch of Nucynta ER, Janssen observed that “Abuse and misuse [are] cited as key issues” in the U.S. long-acting opioid market.⁹⁵⁹

⁹⁵³ JAN-MS-00457581 at 76.

⁹⁵⁴ JAN-MS-00457581 at 94.

⁹⁵⁵ JAN00008227 at 3.

⁹⁵⁶ JAN00008227 at 5.

⁹⁵⁷ JAN00008227 at 20.

⁹⁵⁸ JAN00008227 at 24.

⁹⁵⁹ JAN-MS-00010752 at 25.

453.6. Another slide in the 2011 PowerPoint listed “Less addiction/abuse potential” as the top “payer unmet need” in the U.S. long-acting opioid market.⁹⁶⁰ This item was circled and had a green check mark beside it for emphasis on the slide.

453.7. This point was reinforced by another slide in the same deck listing “Increased use of opioids is associated with increased abuse and diversion” as the highest priority challenge for MCOs [managed care organizations] and PBMs [pharmacy benefit managers].⁹⁶¹

454. A member of Janssen’s medical affairs team pushed back on proposed launch materials that sought to differentiate Nucynta with regards to abuse concerns. In January 2009, shortly after the approval of Nucynta IR and before sales of it had begun, Tanya Nelson, one of Janssen’s Senior Medical Science Liaisons, emailed a 19-bullet-point list of reasons that sections of proposed “Tapentadol 24 Hour Launch Training Workshop” videos needed to be rewritten. Included on the list was “we don’t have data supporting decreased abuse potential,” and “superiority claims in efficacy/safety can’t be made vs oxycodone.”⁹⁶²

455. At her deposition, Roxanne McGregor-Beck, a Johnson & Johnson Director of Regulatory, Advertising and Promotion, testified that she agreed with Nelson’s statement regarding the lack of data supporting decreased abuse potential claims, and noted “[I]t would be inconsistent with our label, and it would be very difficult for them to do so if there was no data to support [decreased abuse potential claims].”⁹⁶³ While Ms. Nelson later wrote that “approval of the workshops is contingent upon the corrections that need to be incorporated into these

⁹⁶⁰ JAN-MS-00010752 at 29.

⁹⁶¹ JAN-MS-00010752 at 42.

⁹⁶² JAN-MS-00469968.

⁹⁶³ Roxanne McGregor-Beck Dep., 57:1-16 (January 17, 2019).

materials,”⁹⁶⁴ I was unable to determine from the record whether her corrections were indeed made.

456. However, once Nucynta was on the market, Janssen continued to understate the risk of abuse by seeking to differentiate its drug as having lower abuse and withdrawal without substantial evidence, and by understating the risk of addiction from opioids in its unbranded advertising.

456.1. In Janssen’s 2012 Nucynta and Nucynta ER Business Plan, Janssen laid out a marketing strategy to “generate data to support lower abuse potential” in order to “strengthen differentiation and value through new & compelling evidence.”⁹⁶⁵

456.2. The 2012 Business Plan further identified “Lower Abuse Potential” as a “Strategic Driver” and proposed abuse potential studies, including a trial against OxyContin. Another slide in the Plan indicated that “Abuse Potential Trial Interim Results” would come in the Second Quarter of 2014.⁹⁶⁶ I can find no evidence in the record that such a trial took place, and Janssen sold Nucynta in early 2015.

456.3. The 2012 “Video Walk –Through” sales aid and script contained a screen shot with a header stating “Make NUCYNTA ER Your Choice for Chronic Pain” along with tabs including “Dual Mechanism of Action,” “Efficacy,” and “Tolerability/Safety/Withdrawal.” Notes underneath the screen shot state, “The low back pain study efficacy, the GI tolerability, and the withdrawal information continue to

⁹⁶⁴ JAN-MS-01124841.

⁹⁶⁵ JAN-MS-00010801 at 12, 42.

⁹⁶⁶ JAN-MS-00010801 at 43, 44.

be the crux of the NUCYTNA ER story, and you should keep reinforcing these critical messages.”⁹⁶⁷

456.4. A SWOT analysis in the 2012 Business Plan, identified among the drug’s strengths “Perceived lower abuse potential for Nucynta? (actionable?).”⁹⁶⁸

456.5. In Janssen’s 2013 Preliminary Business Plan for Nucynta IR and ER, Janssen again put forth “Generate data on comparative effectiveness, efficiency and abuse” as a differentiation strategy.⁹⁶⁹ There is still no indication a comparative study was yet underway.

456.6. In May 2013, despite the fact that the Nucynta ER had not been approved as tamper resistant, Janssen instructed its sales representatives, if asked by customers whether Nucynta was tamper resistant or abuse deterrent, to respond that “The NUCYNTA ER formulation was designed to not be amenable to splitting, crushing, or dissolution,” while also noting that the ability of Nucynta ER “to deter abuse, misuse, or diversion has not yet been established.”⁹⁷⁰

456.7. In a document entitled, “Pain Force District Manager’s meetings with Pharmacy District/Regional Directors” from September 2013, shortly after FDA denied Janssen’s request for TRF labeling, Janssen provided its district managers with a list of Do’s and Don’ts. Under “Don’t,” Janssen advised its sales team, “Don’t: Discuss topics concerning abuse, misuse, and diversion.”⁹⁷¹

⁹⁶⁷ JAN-MS-00774016 at 6.

⁹⁶⁸ JAN-MS-00010801 at 61.

⁹⁶⁹ JAN-MS-00011318 at 7.

⁹⁷⁰ JAN-MS-00658451; JAN-MS-00658452.

⁹⁷¹ JAN-MS-00982914.

456.8. In its 2014 Pain Business Review for Nucynta IR and ER, Janssen claimed that “NUCYNTA ER differentiated on Tolerability and Abuse Potential relative to competition.”⁹⁷²

456.9. The Pain Business Review contained a “NUCYNTA ER Positioning Statement” asserting that Nucynta “offers a superior overall clinical profile because: it provides best-in-class efficacy across multiple pain types... so that: physicians and patients can achieve their individualized pain improvement goals without many of the challenges typically associated with traditional opioids.”⁹⁷³

456.10. Despite the fact that by this time FDA had denied Janssen's request for TRF labeling for Nucynta ER, as noted above, the Pain Business Review identified among the “RTBs [reasons to believe]” for the Positioning Statement the following: “Uses technology designed to make it more difficult to crush, split, and dissolve.”⁹⁷⁴

456.11. From 2013 to 2015, there were 24 sales calls/visits for Nucynta ER that had “withdrawal” included in the key message.⁹⁷⁵

457. Janssen also understated the risk of addiction and withdrawal from opioids in its unbranded website, prescriberresponsibly.com.

457.1. A piece on the website entitled “Use of Opioid Analgesics in Pain Management,” by Keith Candiotti, downplayed the risk of addiction, stating as follows:

Aside from medical issues related to opioid analgesics, there are nonmedical issues that may have an impact on prescribing patterns and patient use of these drugs. Practitioners are often concerned about

⁹⁷² JAN-MS-02389698 at 23.

⁹⁷³ JAN-MS-02389698 at 73.

⁹⁷⁴ JAN-MS-02389698 at 74.

⁹⁷⁵ JAN00118960. No narrative is provided for these call notes so the exact nature of what was discussed is unknown.

prescribing opioid analgesics due to potential legal issues and questions of addiction. By the same token, patients report similar concerns about developing an addiction to opioid analgesics. While these concerns are not without some merit, it would appear that they are often overestimated. According to clinical opinion polls, true addiction occurs only in a small percentage of patients with chronic pain who receive chronic opioid analgesic therapy.⁹⁷⁶

457.2. A number of materials posted on the website minimized the risk of addiction by invoking the concept of pseudoaddiction. For example, in a piece entitled “What a Prescriber Should Know Before Writing the First Prescription,” Heit & Gourlay defined pseudoaddiction as “a syndrome that causes patients to seek additional medications due to inadequate pharmacotherapy being prescribed. Typically when the pain is treated appropriately, the inappropriate behavior ceases.”⁹⁷⁷

458. Janssen also financially supported and worked with pain advocacy organizations that put forth “educational” materials and activities that falsely claimed that the risk of opioid addiction had been exaggerated. Below is a brief summary of Janssen’s involvement in these advocacy organizations and their false and misleading statements:

458.1. From January 2012 through March 2017 Janssen spent \$465,152.85 funding seven different pain advocacy groups.⁹⁷⁸ Those groups are: Academy of Integrative Pain Management, American Academy of Pain Management, American

⁹⁷⁶ *Id.*

⁹⁷⁷ JAN-MS-03090578.

⁹⁷⁸ Fueling an Epidemic: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups. U.S. Senate Homeland Security & Governmental Affairs Committee, Ranking Member’s Office, PPLPC031001561047 at 5. Also available at <https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf>

Chronic Pain Association, American Pain Society, American Society of Pain Management Nursing, The Center for Practical Bioethics, and U.S Pain Foundation.

458.2. The “Marketing Overview Strategic Plan” discussed above shows that Janssen worked with the American Pain Society to “Kick Off Unbranded Campaign” for its Nucynta launch in 2008, and sponsored an APS booth featuring a number of unbranded posters promoting Nucynta.⁹⁷⁹

459. In August, 2007, Will Rowe, the Executive Director of the American Pain Society, wrote to Greg Panico, a Janssen Executive, about APS’s efforts to push back against news stories about abuse and diversion of opioids.

459.1. The email stated:

As you know, the recent AP story about the DEA figures regarding the prescription and use of opioid medicines received wide and, in many cases poorly slanted coverage. The day after the AP release we received a call from NBC News wanting to get our reaction to the AP story. They seemed headed to report in a similar direction fanning concern that there were too many opioid medicines out there causing havoc in the nation. We talked with them extensively about the other side of the story and had them speak to two pain patients and a pain physician.⁹⁸⁰

459.2. Mr. Panico forwarded Mr. Rowe’s email on to other Janssen employees, describing it as “a surprisingly balanced story that addresses value of opioids in treating chronic pain, including statement from Dr. Pamela Palmer at U California that opioids are chemicals like any other medicine and should not have stigma. APF seems to be a strong influencer of positive media coverage of this topic.”⁹⁸¹

⁹⁷⁹ JAN-MS-00457581 at 125.

⁹⁸⁰ JAN-MS-00275814.

⁹⁸¹ *Id.*

459.3. Mr. Panico also asked Ketchum for a copy of the article “to be able to use it at team PR update for tapentadol to show them that there is balanced coverage of this topic.”⁹⁸²

460. In my opinion, Janssen’s promotion of Nucynta misleadingly minimized the risks of abuse and addiction.

VIII. TEVA

A. Overview

461. Teva manufactures and markets various opioid products, including Actiq and Fentora.⁹⁸³

462. Actiq and Fentora are similar products. Both contain fentanyl,⁹⁸⁴ a known *mu*-opioid receptor agonist, and both are considered oral transmucosal fentanyl products.⁹⁸⁵

According to FDA, “Actiq is a lozenge that is presented on a stick making it easily removable from the mouth, while Fentora is a lozenge without a stick.”⁹⁸⁶

463. According to a 2008 FDA memorandum, approval of Actiq and Fentora “represented availability of fentanyl without the necessity of intravenous access.” Accordingly, “FDA had numerous discussions with the sponsors during the development of the products to

⁹⁸² *Id.*

⁹⁸³ The drug sponsor for Actiq was Anesta Corporation, which Cephalon, Inc. acquired in 2000. The drug sponsor for Fentora was Cephalon. Teva acquired Cephalon in 2009. These entities are referred to herein as “Teva.”

⁹⁸⁴ According to the DEA, “Fentanyl is a synthetic opioid that is 80-100 times stronger than morphine.” Available at <https://www.dea.gov/factsheets/fentanyl> (last visited March 25, 2019)

⁹⁸⁵ Oral transmucosal delivery allows for rapid onset of action to occur in less than hour. Actiq FDA Label, December 2016, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020747s043s0441bl.pdf (last visited March 25, 2019); Fentora FDA Label, December 2016. *available at*, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021947s024s0251bl.pdf (available at March 25, 2019)

⁹⁸⁶ PPLP004041768 at 2.

address our [FDA's] concerns regarding the potential for abuse and misuse, and the potential for accidental exposure with these formulations.”⁹⁸⁷

464. To minimize these concerns, “rigorous risk management programs were included as part of the approval of the products” that “were designed to limit the prescribing of these products to opioid tolerant patients with breakthrough pain from cancer with the intent that this would limit the overall prescribing of the medication.”

465. Teva's marketing of Actiq and Fentora ignored strict limitations imposed by FDA, as discussed below.

B. Actiq

1. Approval of Actiq for Limited Use.

466. FDA approved Actiq on November 4, 1998 for the limited indication of “management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.”⁹⁸⁸

467. On February 7, 2007, FDA approved a supplemental NDA, expanding the indication to “only for management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.”⁹⁸⁹ The revised label also included pharmacokinetic data on patients from ages 5 to 15, and stated that “safety and efficacy below age 16 years have not been established.”⁹⁹⁰

⁹⁸⁷ TEVA_MDL_A_02186676 at 1.

⁹⁸⁸ https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/20747ltr.pdf at 5.

⁹⁸⁹ https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/020747s027ltr.pdf at 1.

⁹⁹⁰ https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020747s027lbl.pdf at 1.

468. FDA further required Actiq be “marketed in accordance with the terms of restricted distribution and use described in the Risk Management Program ..., and as recommended in the attached final labeling”⁹⁹¹

2. Teva Marketed Actiq for Non-Malignant Pain, for Which Safety Had Not Been Established by Substantial Evidence.

469. As noted above, Teva’s approved indication limited its use to only breakthrough pain among opioid tolerant patients with malignancies.

470. Teva acknowledged that Actiq’s narrow indication limited its marketability.

470.1. Upon acquiring the rights to Actiq in 2000, Teva reevaluated the business model and promotional activities for the product, issuing a “Master Plan” for Actiq on November 16, 2000 that included the following observation:

From its initial submission, through the approval process, and in the post marketing period, Actiq has been scrutinized especially closely by FDA. The impact is felt most acutely when comparing Actiq claims versus those that our competitors are allowed to make. This comparison leads us to believe that Actiq is currently competing on an “unlevel” playing field, and that a complete examination of our regulatory strategy should be undertaken.⁹⁹²

470.2. In this “Master Plan,” Teva likewise recognized Actiq’s narrow indication, remarking:

This is the very first time than an analgesic has ever been so tightly restricted in terms of a very specific type of pain (breakthrough cancer pain) in a very specific patient population (opioid tolerant patients with malignancies).[...]By the [FDA’s] own admission, these restrictions were established for social considerations and were not derived from any clinical experience.⁹⁹³

⁹⁹¹ TEVA_MDL_A_08242688 at 1.

⁹⁹² TEVA_CHI_00042757 at 40.

⁹⁹³ TEVA_CHI_00042757 at 40.

471. Despite acknowledging Actiq’s narrow indication, Teva developed marketing plans to expand the use of Actiq for non-malignant chronic pain:

471.1. For example, a key strategic recommendation of Teva’s 2000 “Master Plan” included expanding beyond cancer pain to chronic pain, noting “we believe it can continue to grow aggressively into 2001 and beyond by expanding the target physician and patient population to allow penetration of the broad chronic pain market.”⁹⁹⁴ In addition, Teva planned to target pain specialists rather than oncologists as pain specialists are “likely to be a more aggressive writer and rapid adopter of *Actiq*” and these physicians “tend to have patients that are more likely to be truly chronic, with many years of potential usage of the product, either for breakthrough pain **or more generally for other chronic pain conditions.**”⁹⁹⁵

471.2. In Teva’s 2003 Marketing Plan, a key marketing initiative was to increase the awareness of general breakthrough pain—or “BTP” as referred to by Teva—beyond that of the more narrow breakthrough cancer pain market—or “BTCP” market:

Many of our targeted physicians and healthcare providers (e.g., RNs, RPhs) believe that they are managing chronic pain adequately, despite the fact that most pain assessment tools do not include questions or pain scales specific to BTP. BTP must become recognized as a critical component of chronic pain that must be assessed and treated as distinct and separate entity from persistent pain.⁹⁹⁶

471.3. Teva’s 2003 Marketing Plan further noted that “anesthesiologists and other pain specialists who have similar prescribing habits, may not require substantial clinical evidence to implement ACTIQ in numerous disease states **other than**

⁹⁹⁴ TEVA_CHI_00042757 at 5.

⁹⁹⁵ TEVA_CHI_00042757 at 4 (emphasis added).

⁹⁹⁶ TEVA_CHI_00042882 at 39; *see also* TEVA_CHI_00042951 at 32.

BTCP...,⁹⁹⁷ adding that “the disease states that represent the largest growth opportunities for ACTIQ include, but are not limited to osteoarthritis, rheumatoid arthritis, chronic back pain, migraine headaches, complex regional pain syndrome and postherpetic neuralgia. Medical affairs support describing the rationale for a rapid acting opioid would help to drive these uses.”⁹⁹⁸

471.4. Teva’s 2003 Marketing Plan also identified strategies to “develop/renew relationships with KOL in the field of pain management in order for ACTIQ to gain the exposure and support needed to become a first line treatment option for **BTP in both malignant and non-malignant pain.**”⁹⁹⁹

471.5. Teva’s 2004 Marketing Plan identified similar strategies to those described in Teva’s 2003 Marketing Plan.¹⁰⁰⁰

472. Beginning as early as 2001, Teva was informed that Actiq was being prescribed for non-malignant breakthrough pain.

472.1. In May and December of 2001, Teva conducted tracking studies to determine how its product was being used.¹⁰⁰¹ The research found that pain specialists were using Actiq in a wide variety of disease states besides cancer, including lower back pain, osteoarthritis, reflex sympathetic dystrophy, post-trauma, fibromyalgia, adhesions, arachnoiditis, rheumatoid arthritis, and other types of headaches.¹⁰⁰²

⁹⁹⁷ TEVA_CHI_00042882 at 17 (emphasis added).

⁹⁹⁸ TEVA_CHI_00042882 at 17.

⁹⁹⁹ TEVA_CHI_00042882 at 39 (emphasis added).

¹⁰⁰⁰ TEVA_CHI_00042951.

¹⁰⁰¹ TEVA_CHI_00042882 at 15.

¹⁰⁰² TEVA_CHI_00042882 at 16.

472.2. In Teva's 2005 Marketing Plan, Teva reported that "[b]ased on physician reporting, 90% of ACTIQ use is for BTP **outside of cancer**, with the majority of use (55% of total) being for chronic back pain."¹⁰⁰³

472.3. Also in this marketing plan, Teva included the chart below of Actiq use by specialty, noting that "specialty usage tends to fluctuate based on patient presentation and physician recognition of the need for rapid acting or BTCP/BTP. For example, neurology usage tends to be higher for headache (97%) while PCP usage is higher for back pain (81%)."¹⁰⁰⁴

ACTIQ Use by Specialty[^]					
	Anes / Pain	Neuro	PCP	Other	Total
Malignant pain	13%	6%	4%	35%	10%
Back pain	49%	21%	81%	41%	55%
Headache	17%	97%	19%	14%	22%
FMS / MPS *	14%	11%	17%	18%	18%
Arthritis	12%	7%	21%	8%	13%
CRPS **	9%	2%	5%	5%	7%
Neuropathy	10%	9%	21%	12%	12%

472.4. By 2006, chronic back pain represented 38% of the underlying conditions treated with Actiq, while cancer was only 8%.¹⁰⁰⁵

473. Following implementation of Teva's marketing plans, Teva's sales of Actiq increased:

473.1. Actiq's total prescriptions increased substantially each year from 1999 to 2003.¹⁰⁰⁶ Prescriptions in 1999 totaled 5,548 and had increased to 326,078 by 2003.¹⁰⁰⁷

¹⁰⁰³ TEVA_CHI_00043010 at 26 (emphasis added).

¹⁰⁰⁴ TEVA_CHI_00043010 at 26.

¹⁰⁰⁵ TEVA_CHI_00043963 at 51.

473.2. Factory sales of Actiq increased from \$1.8 million in the first quarter of 2000 to \$30.1 million by the second quarter of 2002.¹⁰⁰⁸ By the third quarter of 2004 factory sales had increased to over \$107 million.¹⁰⁰⁹

473.3. Actiq's sales continued to grow with sales totaling \$590.7 million in 2006.¹⁰¹⁰ By 2006 the price had increased to approximately \$1,863.¹⁰¹¹

473.4. The number of Actiq prescribers also increased during in this same time period from 26,200 prescribers in 2000 to 471,068 by 2005.¹⁰¹²

474. In my opinion, Teva marketed Actiq for non-cancer pain, an indication that lacked substantial evidence to support safety.

3. Teva Failed to Comply with its Risk Management Strategies in Marketing Actiq

475. FDA considered the Actiq RiskMap an “integral part of the approved NDA...and is an essential component of the terms of this NDA’s approval by FDA for marketing...”¹⁰¹³ The purpose of the RiskMap was “to ensure the safe use” of Actiq, and “[r]edundancy of the program elements is one measure used to strengthen the effectiveness of the [RiskMap].”¹⁰¹⁴

476. The FDA-mandated RiskMap required the dissemination of “key messages” on “Proper Patient Selection,” including “Actiq is specifically indicated solely for the treatment of

¹⁰⁰⁶ TEVA_CHI_00043010 at 11.

¹⁰⁰⁷ TEVA_CHI_00043010 at 11.

¹⁰⁰⁸ TEVA_CHI_00042882 at 6.

¹⁰⁰⁹ TEVA_CHI_00043010 at 9.

¹⁰¹⁰ TEVA_CHI_00043963 at 45.

¹⁰¹¹ TEVA_CHI_00043963 at 46.

¹⁰¹² TEVA_CHI_00043963 at 47.

¹⁰¹³ Actiq Approval Letter, November 4, 1998
https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/20747ltr.pdf at 2.

¹⁰¹⁴ TEVA_MDL-A-03272088 at 5.

breakthrough cancer pain in chronic opioid tolerant cancer patients,” and on “Prevention of Diversion and Abuse Messages,” including “Actiq may be habit forming.”¹⁰¹⁵ The RMP also included a section on “Professional Medical Education” to deliver safety information and convey the key messages.¹⁰¹⁶

477. The FDA-mandated RiskMap included surveillance and monitoring programs that were designed to “determine the effectiveness of the Actiq Risk Management Program by monitoring [...] potential product use among opioid-non-tolerant populations [...] off-label use [...] and trigger intervention when problems are discovered.”¹⁰¹⁷

478. Teva was further required to “provide a quarterly report to the FDA compiled from all data collected by the methods described under the Actiq Surveillance and Monitoring Program and Interventions. This report will describe and provide data on any concerns for [...] off-label usage.”¹⁰¹⁸

479. As discussed above, Teva’s off-label marketing was contrary to the key messages in the FDA mandated RiskMap concerning proper patient selection and risks of abuse. Moreover, Teva was in possession of voluminous data and information indicating off-label use of Actiq. Rather than intervene and report to FDA, as required by its Risk Management Program, Teva embraced this inappropriate usage or looked the other way.

480. On December 2, 2003, an internal audit with the objective to “audit Actiq Risk Management Program reporting activities to determine compliance with filing requirements”

¹⁰¹⁵ TEVA_MDL_A_03272088 at 6.

¹⁰¹⁶ TEVA_MDL_A_03272088 at 12.

¹⁰¹⁷ TEVA_CHI_00049296 at 22.

¹⁰¹⁸ TEVA_CHI_00049296 at 29.

concluded that “based on the findings of this audit [...] Cephalon is not in compliance with the commitments communicated in the Risk Management Program dated August 1, 2001...”¹⁰¹⁹

481. Afterwards, Teva submitted a supplemental application seeking to change the Actiq RiskMap, which FDA found non-approvable on June 21, 2005.¹⁰²⁰ FDA found that Teva’s proposed changes would “decrease the surveillance of off-label use of Actiq in the face of increasing off-label use by prescribers,” and required that Cephalon “Justify the proposal for decreased monitoring of off-label use of Actiq, and outline effective interventions to discourage it.”¹⁰²¹ Teva never justified its proposal to decrease monitoring for off-label use to FDA, and so no further changes to the Actiq RiskMap were approved.

482. In my opinion, Teva failed to comply with its risk management obligations in marketing Actiq.

C. Fentora

1. Approval of Fentora for Limited Use.

483. The FDA approved Fentora (fentanyl buccal tablet), manufactured by Teva, on September 25, 2006.¹⁰²²

484. Fentora was approved for the “management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.”¹⁰²³ Unlike Actiq, Fentora did not have distribution restrictions placed upon it at approval.

¹⁰¹⁹ TEVA_MDL_A_01159585 at 1

¹⁰²⁰ TEVA_MDL_A_01583458 at 1.

¹⁰²¹ TEVA_MDL_A_01583458 at 1.

¹⁰²² https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021947s000ltr.pdf. The FDA approved Fentora for five dosage strengths, 100, 200, 400, 600, and 900 mcg.

¹⁰²³ https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021947s000ltr.pdf.

2. Teva Promoted Fentora for Non-Malignant Pain, for which it Lacked Substantial Evidence to Support Safety

485. Like Actiq, Fentora had a very narrow labeled indication.

486. Notwithstanding this narrow indication, and the off-label use of Actiq, Teva identified “convert ACTIQ loyalists to FEBT adopters” as a “critical success factor” for Fentora.¹⁰²⁴

487. In its December 2005 Fentora Marketing Plan, Teva stated it planned to convert Actiq loyalists by “leveraging strong relationships and bridging from the solid market conditioning base it established prelaunch.”¹⁰²⁵

488. Teva continued to use the strategy developed for Actiq, specifically continuing to expand the usage of Fentora beyond the appropriate use in break through cancer pain – referred to as BTCP – to off-label use in the broader break through pain – referred to as BTP – market.

489. The 2005 Marketing Plan stated that a “critical success factor” identified for Fentora was to encourage off label use in non-cancer break through pain (BTP), specifically by “continu[ing] to develop BTP market by increasing awareness and understanding of BTP and its optimal treatment.”¹⁰²⁶

490. Like with Actiq, Teva was successful in encouraging off-label use in non-cancer patients. According to a July 2, 2008, Fentora Marketing Overview presentation, by 2007, of approximately 22,000 patients treated with Fentora, cancer patients represented only 18%.¹⁰²⁷

¹⁰²⁴ TEVA_MDL_A_00368405 at 6, 15.

¹⁰²⁵ TEVA_MDL_A_00368405 at 12.

¹⁰²⁶ TEVA_MDL_A_00368405 at 14

¹⁰²⁷ TEVA_MDL_A_01500140 at 41.

“Other pain” was the most frequently treated underlying condition (27%) followed by back pain (20%) and other diagnosis (20%).¹⁰²⁸

491. The same July 2008 marketing presentation reported that in July 2007 pain specialists were writing the most Fentora prescriptions (49%), followed by primary care physicians (22%), and other physicians (20%).¹⁰²⁹ Oncologists wrote only 3% of the prescriptions.¹⁰³⁰ In May 2008, there was a slight decrease in prescribing pain specialists (47%), and an increase in primary care prescribers (23%).¹⁰³¹

492. From September 2007 to December 2008, pain specialists continued to write the most Fentora prescriptions (44%), followed by primary care physicians (21%).¹⁰³² Oncologists continued to rarely write Fentora prescriptions (3%).¹⁰³³ During this time there was an overall decrease in the number of pain specialists prescribing Fentora on a monthly basis.¹⁰³⁴

493. In my opinion, Teva promoted Fentora for non-malignant pain, which lacked substantial evidence to support safety.

¹⁰²⁸ TEVA_MDL_A_01500140 at 41.

¹⁰²⁹ TEVA_MDL_A_01500140 at 59.

¹⁰³⁰ TEVA_MDL_A_01500140 at 59.

¹⁰³¹ TEVA_MDL_A_01500140 at 60.

¹⁰³² TEVA_MDL_A_00398245 at 31.

¹⁰³³ TEVA_MDL_A_00398245 at 31.

¹⁰³⁴ TEVA_MDL_A_00398245 at 31.

IX. ACTAVIS

A. Overview

494. Kadian is the brand name for extended-release oral formulation of morphine sulfate, an opioid analgesic with a release rate-controlling polymer coating marketed by Actavis.¹⁰³⁵

495. The FDA approved Kadian on July 26, 1996 “for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.”¹⁰³⁶

496. Kadian capsules “share the risks of other prescription opioids.”¹⁰³⁷

B. Actavis Promoted Kadian in a Manner that Understated Its Risks, Overstated Its Benefits, and for Indications that Lacked Substantial Evidence to Support Safety and Efficacy.

497. Actavis recognized that “the market for both acute and chronic pain medications [was] increasing, [and] that the chronic pain segment had experienced [] dramatic growth.”¹⁰³⁸

498. The Kadian marketing plan took into account that “over half of the people taking prescription pain medication or over-the-counter drugs [were] NOT satisfied with their current treatment plan,” and that this presented “a significant marketing opportunity for the right drug in the chronic pain market.”¹⁰³⁹

¹⁰³⁵ ALLERGAN_MDL_0007776; ACTAVIS0248829. Actavis acquired Kadian from Alpharma on December 19, 2009 and began marketing it on or around that date. ALLERGAN_MDL_01514893. The specific entities that held the Kadian NDA were: Actavis Elizabeth LLC (December 2008-2013); Actavis Laboratories UT, Inc. f/k/a Watson Laboratories, Inc. – Salt Lake City (2013-2016); and Allergan Sales, LLC (2016-present). Allergan-Kaufhold-003 at 6.

¹⁰³⁶ ACTAVIS0248829 at 1. The Kadian dosages available since introduction have varied, but have included 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg of morphine sulfate. ALLERGAN_MDL_0007774.

¹⁰³⁷ ACTAVIS0248829 at 1.

¹⁰³⁸ ACTAVIS00006930 at 11.

¹⁰³⁹ ACTAVIS00006930 at 11 (emphasis in original).

1. Actavis Promoted Kadian for Indications Broader than Supported by Substantial Evidence and for Which Safety and Efficacy Were Not Established.

499. On February 18, 2010, Actavis received a Warning Letter from DDMAC concerning Actavis's promotional launch materials for Kadian, which included a Co-Pay Assistance Program Brochure and a "PK to PK Comparison Detailer" for Kadian.¹⁰⁴⁰

500. Kadian's PK to PK Comparison Detailer, included the following claims:

- **"Allows for less breakthrough pain and more consistent pain relief for patients"**
- **"Better pain control"**
- **"Allow patients to live in less pain"**
- **"Allow individualization and customization of a patient's pain treatment"**
- **"Prescribe KADIAN – Less pain for your patients. More options for you."**
- **"Less Pain. More Options."**¹⁰⁴¹

501. Similarly, Kadian's Co-Pay Brochure included the following statements:

- **"Why is pain management important?** Pain management is a large part of your overall health care plan. Many Americans suffer from chronic or ongoing pain . . . Managing your pain the right way begins by talking to your healthcare provider. Discover the cause of your pain by taking note of what makes your pain start and what makes it worse."
- **"What is chronic pain?** Chronic pain is ongoing and can last longer than 6 months. Chronic pain can be mild or severe"
- **"How can I treat my chronic pain?** To help manage your pain, your healthcare provider will chose a drug that works just for you."¹⁰⁴²

502. According to FDA, these promotional materials suggested that Kadian would be appropriate for use in broader types of pain than indicated.¹⁰⁴³ FDA found these presentations

¹⁰⁴⁰ ACTAVIS0238310 at 1.

¹⁰⁴¹ ACTAVIS0238310 at 5.

¹⁰⁴² ACTAVIS0238310 at 6.

“particularly concerning considering the serious and potentially fatal risks associated with the drug,” and emphasized that “Kadian is only appropriate for a very limited patient population who experience pain.”¹⁰⁴⁴

503. FDA likewise found that both promotional pieces provided only a partial indication for Kadian, omitting the important limitation that:

KADIAN is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. KADIAN is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate ...¹⁰⁴⁵

504. FDA noted that “the statement, ‘*Please see accompanying complete Prescriber Information*’ [which] appears on various pages of the Comparison Detailer and Co-Pay [Brochure] . . . does not mitigate the implications [these] claims and presentations.”¹⁰⁴⁶

505. Despite FDA’s warning that Actavis should refrain from marketing Kadian for use in broader populations than indicated, Actavis used promotional messages similar to those described.

505.1. For example, Actavis’s sales training for Kadian included a general and expansive definition of pain that was not focused on the “moderate to severe” pain threshold that Kadian was intended to treat.¹⁰⁴⁷ The sales training materials appear to have been in continuous use until at least 2013.¹⁰⁴⁸

¹⁰⁴³ *Id.*

¹⁰⁴⁴ *Id.*

¹⁰⁴⁵ *Id.*

¹⁰⁴⁶ *Id.* (emphasis in original).

¹⁰⁴⁷ ALLERGAN_MDL_01610522 at 8.

¹⁰⁴⁸ See ALLERGAN_MDL_01610520 (indicating date and circulating Kadian Training Manual);

505.2. The misleading messaging identified in FDA’s warning letter was used by Actavis both in the sales training materials and the marketing materials at issue in the DDMAC letter.¹⁰⁴⁹

506. In my opinion, Actavis promoted Kadian for indications broader than supported by substantial evidence and for which safety and efficacy were not established.

2. Actavis Overstated the Benefits of Kadian with Respect to Functionality and Quality of Life.

507. The Co-Pay Brochure that Actavis used for promotion of Kadian included the following presentations:

- “. . . Many Americans suffer from chronic or ongoing pain. It can cause you to miss work and can even keep you from enjoying life. If left untreated pain can place stress on your body and your mental health. . . .”
- “. . . Chronic pain . . . can be inconvenient and can keep you from your daily tasks.”¹⁰⁵⁰

508. As indicated in the DDMAC Letter above, FDA found that these representations constituted unsubstantiated effectiveness claims, explaining that it is “not aware of substantial evidence or substantial clinical experience demonstrating that the magnitude of the effect the drug has in alleviating pain, taken together with any drug-related side effects patients may experience (such as the common adverse events of drowsiness, dizziness, constipation and nausea) results in an overall positive impact on a patient’s work, physical and mental functioning, daily activities, or the enjoyment of life.”¹⁰⁵¹

¹⁰⁴⁹ See ALLERGAN_MDL_01234652.

¹⁰⁵⁰ ACTAVIS0238310 at 10.

¹⁰⁵¹ ACTAVIS0238310 at 11.

509. In addition, FDA noted it was “not aware of any studies demonstrating that the level of pain reduction experienced by patients on Kadian therapy corresponds with a positive impact on the outcomes claimed.”¹⁰⁵²

510. In my opinion, Actavis’s promotional materials overstated the benefits of Kadian with respect to patient functionality and quality of life.

(a) Actavis Falsely Marketed Kadian as Safer and More Effective than Other Opioid Products.

511. As indicated in the DDMAC Letter, Actavis’s Comparison Detailer misleadingly implies “that Kadian has been shown to be superior to MS Contin and generic controlled-release morphine because Kadian’s pharmacokinetic properties will lead to less to less breakthrough pain and more consistent pain relief.”¹⁰⁵³

512. Specifically, the Comparison Detailer includes the following claims:

- **“Why settle for generic MS Contin tablets . . . When you can prescribe the benefits of Kadian capsules?”**
- **“Fewer peaks and valleys
Smooth steady state plasma levels compared with controlled-release (CR) morphine tablets q12h and q24h.”**
- **“Allow for less breakthrough pain and more consistent pain relief for patients.”**

513. For support of the above claims, the Comparison Detailer cites to current Kadian prescribing information and to Geoffrey, *et. al.*, *Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly Ms Contin in the treatment of severe cancer pain*, 69 Pain 295–302 (1997).¹⁰⁵⁴ However, FDA stated it was not “aware of any

¹⁰⁵² *Id.*

¹⁰⁵³ ACTAVIS0238310 at 7.

¹⁰⁵⁴ *Id.*

substantial evidence or substantial clinical experience that supports these claims and presentations.”¹⁰⁵⁵

514. In addition, as the DDMAC Letter indicated, “the Comparison Detailer include[d] the following pain and sleep-related claims and presentations that compare[d] Kadian to MS Contin and generic controlled-release morphine:

- **‘Better pain control and improved sleep scores’**
- **‘Improved pain control and sleep scores in patients treated with KADIAN who were previously on CR morphine tables’**
- **‘Allow patients to live with less pain and get adequate rest with less medication’**”¹⁰⁵⁶

515. FDA found that Actavis supported these claims by citing to “a historically controlled study of inadequate design, completely lacking any concurrent control.”¹⁰⁵⁷ FDA reiterated that it was “not aware of any substantial evidence or substantial clinical experience to support such a claim.”¹⁰⁵⁸

516. FDA also noted that “the Comparison Detailer include[d] the following dosing claims and presentations that compare Kadian with both MS Contin and AVINZA (morphine sulfate extended-release capsules, CII (Avinza):

- **‘Fewer barriers to prescribing...[t]he unique dosing flexibility of KADIAN gives you more options with a morphine’**
- ‘Claims below the chart include the following:
 - **No immediate-release (IR) component**
 - **No ceiling dose – contains no acetaminophen, ibuprofen, or fumaric acid**
 - **Allows for titration in increments of 10 mg, with a low dose**

¹⁰⁵⁵ *Id.*

¹⁰⁵⁶ ACTAVIS238310 at 8 (emphasis in original).

¹⁰⁵⁷ ACTAVIS238310 at 9.

¹⁰⁵⁸ *Id.*

- of 10 mg
- **Allow individualization and customization of a patient’s pain treatment”**¹⁰⁵⁹

517. FDA further stated, “These claims are misleading because they imply that Kadian is superior to both MS Contin and Avinza because Kadian’s dosage strength...offers ‘fewer barriers to prescribing,’ and because Kadian has no immediate release component, no ceiling dose, and allows for 10 mg titration increments.”¹⁰⁶⁰ “FDA again noted that it was “unaware of any substantial evidence or substantial clinical experience to support the claim that the above dosing characteristics allow Kadian to have ‘fewer barriers to prescribing’ (the meaning of which is not clear) as compared to other extended-release morphine products.”¹⁰⁶¹

518. A training brochure used by the Actavis sales team as of December 14, 2009 made similar comparisons to those criticized as improper in the DDMAC letter.¹⁰⁶²

519. Actavis’s sales representatives were trained to make misleading statements, unsupported by substantial evidence, that Kadian had lower abuse potential as compared to other opioid products, including the following claims:

“KADIAN patients experience sustained morphine release with less fluctuations vs. morphine sulfate.”

“KADIAN patients report improved management of pain vs. morphine sulfate.”

¹⁰⁵⁹ ALLERGAN_MDL_00813589 at 4 (emphasis in original).

¹⁰⁶⁰ *Id.*

¹⁰⁶¹ *Id.*

¹⁰⁶² Compare ACTAVIS0799208 (criticizing the comparison “Fewer peaks and valleys” and comparison graphs) with ALLERGAN_MDL_01234657 (the same comparison); compare ACTAVIS0799209 (criticizing the comparison “Better pain control and sleep scores” and comparison graphs) with ALLERGAN_MDL_01234658 (the same comparison); compare ACTAVIS0799211 (criticizing the comparison “Fewer barriers to prescribing” and subsequent explanatory text) with ALLERGAN_MDL_01234656 (the same comparison and similar explanatory text).

“KADIAN patients require less rescue medication vs. morphine sulfate.”¹⁰⁶³

520. Even after receipt of the DDMAC letter, Actavis’s sales representatives continued to be trained to make misleading statements, unsupported by substantial evidence, that Kadian provided steady blood levels of morphine and “few peaks and valleys.”

389.1 A November 2011 sales team training PowerPoint trained Actavis’s sales representatives to utilize the statement that: “Kadian provides steady blood levels of morphine sulfate with few peaks and valleys.”¹⁰⁶⁴

389.2 March 2013 marketing sales training presentation instructed: “Kadian provides steady blood levels with few peaks and valleys (show PK charts from Detail Aid)”¹⁰⁶⁵

389.3 A February 2013 Kadian Sales Training Presentation stated: “Kadian provides steady blood levels of morphine sulfate with few peaks and valleys.”¹⁰⁶⁶

389.4 A September 13, 2012 Kadian Marketing Update likewise instructed: “Experience sustained morphine release with less fluctuations vs. morphine sulfate” “Report improved management of pain vs. morphine sulfate.

¹⁰⁶³ ALLERGAN_MDL_00020454 at 47.

¹⁰⁶⁴ ACTAVIS0335094 at 10.

¹⁰⁶⁵ ACTAVIS0000564 at 27 and 30.

¹⁰⁶⁶ ALLERGAN_MDL_00001525 at 21.

Require less rescue medication vs. morphine sulfate.”¹⁰⁶⁷ “Kadian provides steady blood levels of morphine sulfate with few peaks and valleys.”¹⁰⁶⁸

521. Actavis received reports that the message that Kadian had “low abuse potential” was delivered to prescribers:

382.1. A September 2011 Kadian Prescriber Research report from an in-depth blinded telephone interview conducted with 12 high volume prescribers of long-acting opioids stated that prescribers reported that Kadian’s strengths included its “low abuse potential.”¹⁰⁶⁹

382.2. “Among those interviewed, Kadian represent[ed] a leading choice of LAO therapy” and was “cited by several as the #1 choice” because of its “low abuse potential” among other reasons.¹⁰⁷⁰

382.3. A September 13, 2012 Kadian Marketing Update, similarly stated that “called-on physicians” reported a perception that Kadian had “low abuse potential.”¹⁰⁷¹

522. In my opinion, Actavis falsely marketed Kadian as safer and more effective than other opioid products.

(b) Actavis Misleadingly Promoted Kadian as Having No Alcohol-Induced Dose Dumping Effect.

523. In 2007, Actavis supported an open-label, in vivo study of the “interaction between Kadian and alcohol” “among 32 healthy male volunteers.”¹⁰⁷² The results of the study

¹⁰⁶⁷ ALLERGAN_MDL_00072907 at 5.

¹⁰⁶⁸ ALLERGAN_MDL_00405512 at 11.

¹⁰⁶⁹ ACTAVIS0268659 at 2-8.

¹⁰⁷⁰ ACTAVIS0268659 at 23

¹⁰⁷¹ ALLERGAN_MDL_00072907 at 3.

¹⁰⁷² ALLERGAN_MDL_01741520.

were presented in The Journal of Pain in April 2008, in an article titled *Effect of Concomitant Ingestion of Alcohol on the In Vivo Pharmacokinetics of KADIAN (Morphine Sulfate Extended Release) Capsules*.¹⁰⁷³

524. According to a summary prepared by Actavis, “[t]he study was undertaken in response to: [t]he withdrawal of Palladone (hydromorphone hydrochloride extended-release) from the market in 2005 after pharmacokinetic data revealed a risk of alcohol-induced dose-dumping” and “[r]ecommendation made by the FDA to further investigate the possibility that other sustained-release narcotics could pose the same danger as Palladone.”¹⁰⁷⁴

525. Actavis claimed that “Although it is recommended that alcohol not be used while the patient is taking opioids, results of this in vivo study indicate that the risk of alcohol-induced dose-dumping in connection with the use of KADIAN is negligible.”¹⁰⁷⁵

526. Actavis instructed its sales force to make promotional claims based on this single-open label study. A single open label study does not constitute substantial evidence in which to draw promotional claims.¹⁰⁷⁶ An Actavis summary of key talking points for the open-label study stated:

- KADIAN is the only extended release opioid product to have demonstrated in vivo that there is no dose dumping¹⁰⁷⁷ of morphine sulfate when taken with

¹⁰⁷³ *Id.*

¹⁰⁷⁴ ALLERGAN_MDL_00438794 at 1.

¹⁰⁷⁵ *Id.* at 11.

¹⁰⁷⁶ In promotion, treatment claims must generally be supported by “substantial evidence” or “two, adequate and well-controlled trials.” An open-label clinical trial is insufficient to satisfy this requirement. 21 U.S.C. § 355(d)(“substantial evidence” means evidence consisting of adequate and well-controlled investigations...) (emphasis added).

¹⁰⁷⁷ Dose-dumping “is the unintended, rapid release of a clinically-significant fraction of a drug substance from a modified-release formulation. Depending on the therapeutic index of a drug, dose-dumping can pose a significant risk to patients due to safety issues, diminished efficacy, or both. Generally, dose-dumping is due to a compromise of the mechanism that retards the rate of drug substance release from the formulation.” ALLERGAN_MDL_00947173 at 3.

alcohol”¹⁰⁷⁸

- “Other products (e.g., AVINZA, OPANA ER, EMBEDA) in the class carry serious warnings regarding concomitant use with alcohol”¹⁰⁷⁹
- “Although it is recommended that alcohol not be used while the patient is taking opioids, results of this in vivo study indicate that for patients requiring therapy for management of moderate to severe pain, in whom consumption of alcohol may occur, KADIAN may represent the safest choice”¹⁰⁸⁰

527. Actavis’s training materials also indicated that AVINZA, OPANA ER, and EMBEDA included Black Box warnings concerning alcohol consumption while KADIAN did not.¹⁰⁸¹

528. In an email dated October 15, 2009, Nathalie Leitch, Director, Specialty Rx at Actavis, indicated to Christine Balogh, Vice President Client Development at CHS consulting, and others that Actavis and its sales team “[were] looking to leverage results from a study that Actavis did which looked at the effects of alcohol on Kadian [pharmacokinetics].”¹⁰⁸² Ms. Leitch “attached a copy of [*Effect of Concomitant Ingestion of Alcohol on the In Vivo Pharmacokinetics of KADIAN (Morphine Sulfate Extended Release) Capsules*] along with a StatGram that Actavis sent out summarizing the results of the study.”¹⁰⁸³ She noted that “Kadian is the only product in the category that has done such a study and which can make the ‘no dose dumping in the presence of alcohol’ claim – we think this is a significant differentiator and would like to incorporate this message into the overall Kadian safety message.”¹⁰⁸⁴

¹⁰⁷⁸ ALLERGAN_MDL_00438794 at 1.

¹⁰⁷⁹ *Id.*

¹⁰⁸⁰ *Id.*

¹⁰⁸¹ *Id.* at 2-10.

¹⁰⁸² ALLERGAN_MDL_01741504 at 1.

¹⁰⁸³ *Id.*

¹⁰⁸⁴ *Id.*

529. Actavis opted to use the open-label alcohol study as part of its marketing to prescribers, because it would be a “significant differentiator” for Kadian to be able to be the only long-acting opioid that could make a “no dose dumping in the presence of alcohol claim.”¹⁰⁸⁵ Moreover, Actavis’s salespeople “use[d] the results to talk about Kadian to prescribers.”¹⁰⁸⁶

530. In her deposition testimony, Ms. Leitch confirmed that Actavis stopped using the alcohol study and StatGram after it received the DDMAC letter in February 2010.¹⁰⁸⁷

531. More than one year after Actavis stopped using the alcohol study and StatGram, market research conducted by Genesis on behalf of Actavis found that prescribers still perceived “lack of potency loss” as a strength for Kadian for “suspected alcohol abusers” and even those with “remote issues of alcohol abuse.”¹⁰⁸⁸

532. As revealed by the Genesis market research, prescribers continued to believe Actavis’s dose dumping claims and that Kadian was safe to use with alcohol.¹⁰⁸⁹

533. In my opinion, Actavis falsely promoted Kadian as having no alcohol-induced dose-dumping effect, and failed to take reasonable measures to correct prescriber misperceptions that persisted even after Actavis ceased using this claim in its promotion of Kadian.

¹⁰⁸⁵ See ALLERGAN_MDL_01741504; Nathalie Leitch Dep., 245:16-247:5. (January 22, 2019)

¹⁰⁸⁶ Nathalie Leitch Dep., 246:17-247:5 (January 22, 2019)

¹⁰⁸⁷ *Id.* at 247:12 -248:19 (“After we got the letter from the FDA, we narrowed everything down to stick within the label.”)

¹⁰⁸⁸ See ALLERGAN_MDL_00399112, ALLERGAN_MDL_00399113 at 8-9; Nathalie Leitch Dep. ,250:8-255:21 (January 22, 2019)

¹⁰⁸⁹ *Id.*

3. Actavis's Promotion of Opioids Minimized the Risks of Addiction and Abuse.

534. Allergan's promotion minimized the addiction potential of Kadian and opioids in general.

534.1. For instance, Actavis decided not to submit the sales training manual to FDA after receipt of the DDMAC letter. Instead, it added a stamp on each page of the July 1, 2010 manual that read: "For Internal and Training Purposes Only: Not to be Distributed."¹⁰⁹⁰

534.2. Further, Actavis indicated in a Kadian Stocking Offer that:

"Concerns about abuse, addiction, and diversion, should not, however, prevent the proper management of pain."¹⁰⁹¹

534.3. Actavis also trained its salespeople with the same message in a take-home study aid.¹⁰⁹²

535. According to Actavis's marketing director Jennifer Altier, the *Kadian Learning System* was "what a [sales] rep would have received upon joining the company, to learn about Kadian and the pain environment."¹⁰⁹³ Among other things, the *Kadian Learning System* discussed "pseudoaddiction."

536. Kadian sales representatives were trained that Kadian users who were "pseudoaddicted" could be differentiated from individuals with "physical dependence,"

¹⁰⁹⁰ Acquired_Actavis_00365380; Jennifer Altier Dep., Ex. 2 (August 2, 2018).

¹⁰⁹¹ Acquired_Actavis_00369188.

¹⁰⁹² ALLERGAN_MDL_01610522 at 109. ("Concern[s] about abuse, addiction, and diversion should not prevent the proper management of pain.")

¹⁰⁹³ Jennifer Altier Dep., 103:10-13 (August 2, 2018).

“tolerance,” and “addiction”¹⁰⁹⁴ based upon their treatment for pain. For example, take-home study aids provided to Kadian sales representatives stated:

“The problem is even more complex because some patients who are undertreated for their physical pain show the symptoms of “pseudoaddiction.” Pseudoaddiction is a set of behaviors (Table 1-3) that are exhibited by patients with inadequately treated pain, including patients with cancer pain. Pseudoaddictive behaviors are not signs of substance abuse, but rather should be considered symptoms of inadequate treatment.”¹⁰⁹⁵

537. In my opinion, Actavis’s promotion of opioids minimized the risks of addiction and abuse.

X. MALLINCKRODT

A. Overview

538. Since 1993¹⁰⁹⁶, Mallinckrodt¹⁰⁹⁷ has sold and promoted various generic and branded opioid products. Mallinckrodt’s branded opioid products included Exalgo and Xartemis XR, and its generic products included oxycodone hydrochloride ER tablets (generic OxyContin), morphine sulfate ER tablets (generic MS Contin), generic fentanyl, generic fentanyl citrate.

539. In addition, Mallinckrodt sold and promoted various opioid addiction treatment products, such as methadone, and acknowledged the significant risk of misuse, abuse, addiction, and overdose associated with opioids.¹⁰⁹⁸

¹⁰⁹⁴ Acquired_Actavis_00188875 at 7.

¹⁰⁹⁵ ALLERGAN_MDL_00439499 at 34.

¹⁰⁹⁶ See Schedule 8.

¹⁰⁹⁷ Maillinckrodt Inc. was a subsidiary of Covidien PLC until June 28, 2013, and for purposes of this report, references to Mallinckrodt incorporate Covidien as well.

¹⁰⁹⁸ MNK-T1_0001279950 at 8. Indeed, as Mallinckrodt’s sales of its opioid products increased, Mallinckrodt recognized a growth opportunity for its addiction treatment products because of the “large and growing problem” of opioid abuse. See MNK-T1_1332076 at 4; MNK-T1_0001179053; MNK-T1_0001179054; MNK-T1_0001179057; MNK-T1_0001961222.

540. Nonetheless, Mallinckrodt utilized marketing tactics that understated risks, overstated benefits, and for indications that lacked substantial evidence to support their safety and efficacy.

B. Exalgo

541. Exalgo is an extended-release hydromorphone oral tablet. Hydromorphone is a “semi-synthetic, hydrogenated ketone of morphine which acts on the u-opioid receptors.”¹⁰⁹⁹

542. Mallinckrodt acquired the rights to distribute Exalgo from Neuromed in June 2009,¹¹⁰⁰ and received FDA approval to market Exalgo ER 8, 12, 16-mg tablets for “the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock analgesia for an extended period of time” on March 1, 2010.¹¹⁰¹ A higher, 32-mg dose of Exalgo was approved in 2012.

543. From 2010 to 2017, Mallinckrodt’s sales of Exalgo exceeded \$717 million dollars.¹¹⁰²

1. Mallinckrodt’s Marketing Strategy for Exalgo

544. With Exalgo, Mallinckrodt’s marketing strategy for Exalgo identified an opportunity to market an extended release hydromorphone tablet to compete with OxyContin and Opana ER.¹¹⁰³ As noted in the 2011 Exalgo Marketing Plan:

The extended-release opioid market as defined above generated sales of \$6.6 billion in 2009. Sales volume is increasing by 9.5%. Within this market,

¹⁰⁹⁹ MNK-T1_0001561047 at 11.

¹¹⁰⁰ See Press Release, “Covidien Announces License Rights Acquisition Agreement,” Medtronic plc (June 17, 2009), available <http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=2003878>.

¹¹⁰¹ Exalgo Approval Letter, March 2010, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021217s000ltr.pdf (last visited March 24, 2019).

¹¹⁰² See Exhibit 5 to Mallinckrodt’s Supplemental Responses and Objections to Interrogatories Nos. 1, 5, 7, 8, 9, 16, 21, 22, 23, 27, 30, 31, 32, 33, and 35, dated January 30, 2019.

¹¹⁰³ MNK-T1_0000708777

OxyContin is the clear market leader with sales of \$3.0 billion in 2009 and 46% market share.... As expected, the branded products, because of their higher price, account for about 62% of market sales. This share will increase in 2010 as generic oxycodone ER products are no longer available.¹¹⁰⁴

545. In introducing Exalgo, Mallinckrodt also noted the minimal competition it would face from generic competition, stating “[i]t is easy to see strategically why we have chosen this market”:

The largest dollar volume is consistent with the prescription volume although certainly as a consequence of minimal generic intrusion, OxyContin represents the largest dollar volume. It is important to point out that despite Opana ER's 3% volume it translates into nearly \$300 MM. It is easy to see strategically why we have chosen this market.¹¹⁰⁵

546. A key Mallinckrodt strategy in entering the extended-release market, according to a 2010 marketing presentation, included targeting “high volume prescribers.”¹¹⁰⁶

2. Mallinckrodt Promoted Exalgo in a Manner that Understated its Risks and Overstated its Benefits

(a) Mallinckrodt Falsely Promoted Exalgo as Safer than other Opioid Products

547. As noted above, Exalgo is extended-release hydromorphone, and hydromorphone is known to have a high abuse potential and an abuse liability similar to other opioids.

547.1. The FDA Medical Reviewer in its review of Exalgo stated that “[f]rom the perspective of risk, the safety data submitted were generally consistent with those of the opioid class of drugs,” and “[t]he risks (including overdose, misuse and abuse) associated with this potent extended-release opioid appear similar to other opioids in this class.”¹¹⁰⁷

¹¹⁰⁴ MNK-T1_0001191100 at 15.

¹¹⁰⁵ MNK-T1_0000255243 at 16.

¹¹⁰⁶ MNK-T1_0000255243 at 33-34.

¹¹⁰⁷ MNK-T1_0001561047 at 8.

547.2. FDA additionally noted in its Medical Review of Exalgo that

“[h]ydromorphone has a high abuse potential at least comparably or slightly higher than oxycodone”; “[t]he PK/PD profile of altered Exalgo (8mg dosage) is similar to that of hydromorphone immediate release (8mg dosage);” “Exalgo has a high abuse potential ...,” and “Exalgo would be predicted to have high levels of abuse and diversion.”¹¹⁰⁸

548. In developing the marketing strategy for Exalgo, Mallinckrodt identified abuse and addiction as major concerns among healthcare providers and patients.

548.1. Pre-market research revealed healthcare providers were concerned about the abuse potential of opioids in addition to efficacy and availability. With respect to patients, the research found that while chronic pain had a profound impact on daily life, patients were concerned about addiction and resentful about having to take the opioids.¹¹⁰⁹

548.2. In an Exalgo Brand Strategy presentation dated April 27, 2010, Mallinckrodt acknowledged the “[n]egative perceptions of hydromorphone: old, too potent, and street value (abuse),” as a barrier to the launch of Exalgo, and planned to “Reposition Hydromorphone” by, among other things, “[d]riv[ing] understanding of the clinical data, differentiating EXALGO in the process.”¹¹¹⁰

549. As with Purdue, Mallinckrodt claimed that Exalgo was superior to other opioid products because of the elimination of the “peaks and troughs.”

¹¹⁰⁸ MNK-T1_0001561047 at 8.

¹¹⁰⁹ MNK-T1_0000861442; *see also* MNK-T1_0000861227 at 1 (doctor is “[e]xtremely concerned about safety and abuse since pill can be crushed, chewed. They are wondering why we didn’t use new technology to prevent this.”).

¹¹¹⁰ MNK-T1_0000255243 at 476.

549.1. For example, in the Mallinckrodt presentation from April 27, 2010, discussed above, Mallinckrodt described how it could reposition Exalgo as a “safe and effective” product:

EXALGO Brand Strategy

Establish EXALGO as a leading safe and effective treatment for chronic pain through **repositioning hydromorphone** with the consistent and steady pharmacokinetic profile of EXALGO, **driving successful** prescriber and patient experience with **safe and appropriate** use and the development of **product advocacy** through thought leader support.¹¹¹¹

549.2. In this same presentation, Mallinckrodt described an Exalgo sales aid that “[c]ompare[s] the steady-state plasma concentrations of EXALGO to those IR formulations,” noting that “[e]specially compelling is the reduction of peaks and troughs.”¹¹¹²

549.3. In a 2011 Marketing Plan, Mallinckrodt’s positioning statement for Exalgo focused on the benefits from its pharmacokinetic profile:, stating that Exalgo “eliminates the peaks and troughs” and provides “smooth, steady hydromorphone blood levels” “resulting in once-daily predictable chronic pain relief.”¹¹¹³

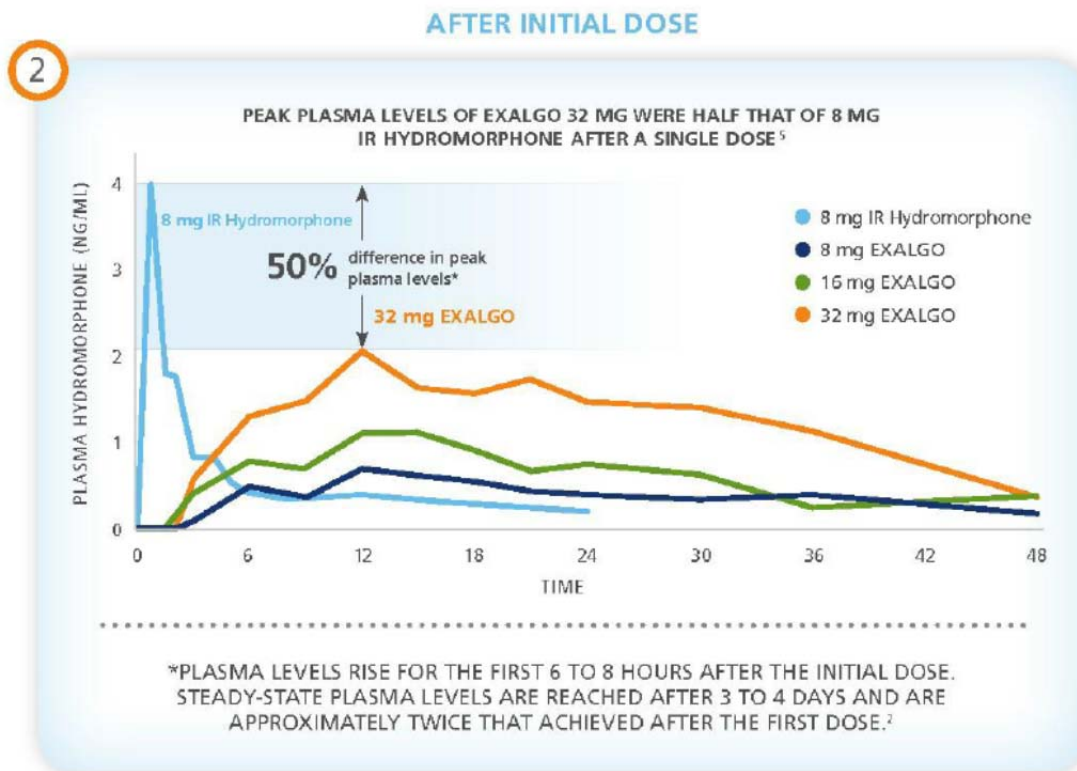
549.4. For example, in a “Master Sales Aid Implementation Guide,” Exalgo sales representatives were told to use the graph below “to show there was a 50% difference in peak concentration after the initial dose” as compared to hydromorphone.¹¹¹⁴

¹¹¹¹ MNK-T1_0000255243 at 48 (original emphasis).

¹¹¹² MNK-T1_0000255243 at 66.

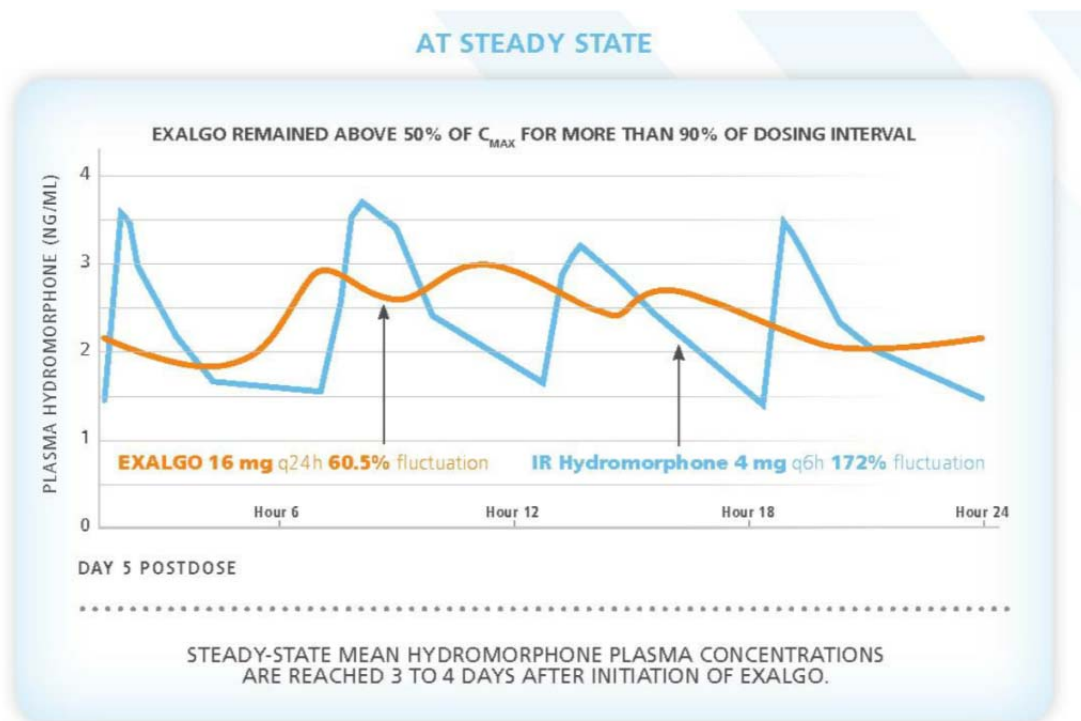
¹¹¹³ MNK-T1_0001191100 at 28.

¹¹¹⁴ MNK-T1_0000742073 at 5.



549.5. The guide also included the following with the instruction “with this graph, your physician will see the sharp contrast between the plasma concentrations of IR hydromorphone (blue line) and Exalgo at steady state (orange line). The IR hydromorphone was dosed 4 times a day and had 172% fluctuation, whereas once-daily Exalgo had only a 60.5% fluctuation.”¹¹¹⁵

¹¹¹⁵ MNK-T1_0000742073 at 5. This graph is included in the 2016 version of the Exalgo label.



549.6. In addition to comparing Exalgo to hydromorphone, Mallinckrodt's Master Sales Aid and Implementation Guide for Exalgo also instructed its sales force to state "our data indicate that Exalgo patients receive a much lower daily morphine equivalent dose than Opana ER and OxyContin patients – 78% lower than Opana ER and 92% lower than OxyContin," which falsely suggested that Exalgo was safer and more efficacious than Opana ER and OxyContin.¹¹¹⁶

549.7. A script for a Mallinckrodt paid speaker also made reference to Exalgo's peak and troughs, comparing them to immediate-release hydromorphone and again noting "[l]ess fluctuations appear in the plasma":

Slide number 6 reviews some of the ways we might attempt to treat pain using medications. On the right hand side of the slide, there are three types of medications portrayed. The first is if somebody is using a typical short-acting opioid given on a q. 6 hour dosing and the classic peak and trough presentation is seen. Even in a steady state situation, there will be

¹¹¹⁶ MNK-T1_0000742073 at 7.

significant fluctuations in peak and trough during the course of the day if someone is only using an immediate release drug.

The second graph shows the plasma concentrations of an individual on a q. 12 hour dosing drug. And you'll notice that there are still peaks and troughs, though less than what are seen in the q.i.d. delivered drug. The final graph at the bottom is someone taking a q. 24 hour drug. Less fluctuations appear in the plasma.¹¹¹⁷

550. In my opinion, Mallinckrodt falsely promoted Exalgo as safer than other opioid products.

(b) Mallinckrodt's sales training misleadingly minimized the risks associated with higher doses of opioids and encouraged sales representatives to make misleading claims regarding abuse deterrence

551. After receiving FDA approval for a higher, 32 mg dose of Exalgo, Mallinckrodt's sales of this dose failed to meet expectations, with a Regional Sales Manager for Exalgo stating on March 27, 2013, "[w]e have to shift as much business, when clinically needed, to 32mg as soon as possible to protect the brand," which faced generic competition for its lower doses.¹¹¹⁸

552. Mallinckrodt told its sales force that the dose of Exalgo could be adjusted upward without identifying the potentially fatal risks of respiratory depression and the increased risk of abuse. For example, in a May 11, 2012 email to Mallinckrodt's sales force, Mallinckrodt provided a sales training song by "Propah Dose by the Might Converters" to "[g]et INSPIRED" to sell Exalgo.¹¹¹⁹ In introducing the song, two actors—"Mike" and "Melissa"—stated: "We hope you have embraced the new INSPIRE messaging and are gaining your customer's attention by being bold and setting EXALGO apart as an innovative delivery system for treating chronic pain." The song told sales representatives to "[m]ake sure you don't stop" increasing the dose of

¹¹¹⁷ MNK-T1_0000100452 at 4.

¹¹¹⁸ MNK-T1_0000124624 at 1.

¹¹¹⁹ MNK-T1_0004610227 at 1.

Exalgo “[c]ause your patient needs relief, mon” but did not identify the risks of increasing the dose of Exalgo:

You can start at the middle
You can start at the top
You can start with very little
But that’s not where you should stop
Cause your patient needs relief, mon
...
So when you start at the middle
Or you start at the top
Or you start with a little
Make sure you don’t stop
Cause your patient needs relief, mon¹¹²⁰

553. Mallinckrodt also told its sale force to highlight Exalgo’s physio-chemical properties to physicians despite Exalgo’s lack of FDA approval as an abuse-deterrent opioid product. For instance, an April 18, 2013 update stated:

Do not proactively discuss this announcement with your customers . . . If your customers ask if EXALGO is abuse deterrent: Ensure the physician understands that EXALGO cannot claim abuse/tamper resistance, but there are physical properties to the tablet of which they should be aware. “Doctor, while we can make no claims concerning abuse potential, you may be interested to know that there are several interesting physical properties of EXALGO. It has a hard outer shell that is difficult to crush. If a tablet is crushed it forms large particles. Also, it agglomerates when exposed to water when crushed. Of course, it is important to keep EXALGO out of the hands of inappropriate patients. However, let’s discuss an appropriate patient for EXALGO like the Elaine patient. This is a patient you likely see multiple times a day who may benefit from the true 24-hour dosing EXALGO provides.”¹¹²¹

554. In my opinion, Mallinckrodt’s sales training misleadingly minimized the risks associated with higher doses of opioids and encouraged sales representatives to make misleading claims regarding abuse deterrence.

¹¹²⁰ MNK-T10004166098 at 1-2.

¹¹²¹ MNK-T1_0000122999 at 1-2.

**(c) Mallinckrodt Misleadingly Minimized the Risk of Addiction
and Funded the CARES Alliance, Which Likewise
Understated the Risk of Addiction**

555. Mallinckrodt understated the risk of addiction through unbranded promotion and the CARES Alliance.

555.1. According to a May 14, 2014 email, Mallinckrodt maintained unbranded Pain Management pocketcard sets for distribution at trade shows.¹¹²² Under the heading “[g]eneral [a]pproach to [p]ain [m]anagement,” the pocketcards told healthcare providers “[a]ddiction rarely occurs unless there is a hx of abuse.”¹¹²³

555.2. Similarly, *Defeat Chronic Pain Now!*,¹¹²⁴ sponsored by Mallinckrodt and positioned as an important source of information for patients¹¹²⁵ understated the risk of addiction, stating “[w]hen chronic pain patients take opioids to treat their pain, they rarely develop a true addiction and drug craving;” “[t]he bottom line: Only rarely does opioid medication cause a true addiction when prescribed appropriately to a chronic pain patient who does not have a prior history of addiction;” and “[h]ere are the facts. It is very uncommon for a person with chronic pain to become ‘addicted’ to narcotics IF (1) he doesn’t have a prior history of any addiction and (2) he only takes the medication to treat pain.”¹¹²⁶

¹¹²² MNK-T1_0002159712.

¹¹²³ MNK-T1_0001531484 at 1.

¹¹²⁴ GALER, BRADLEY & C. ARGOFF., *DEFEAT CHRONIC PAIN NOW!* (2010).

¹¹²⁵ The CARES Alliance catalogue listed *Defeat Chronic Pain Now!* as a “Patient Tool.” MNK-T1_0001493093 at 13; *see also* (MNK-T1_0000098099) (“Example of Education and Enabling Tools” “Patient” “Defeat Chronic Pain Now”)

¹¹²⁶ GALER, BRADLEY & C. ARGOFF., *DEFEAT CHRONIC PAIN NOW!* (2010) at 176-178.

556. In my opinion, Mallinckrodt misleadingly minimized the risk of addiction and funded the CARES Alliance which likewise understated the risk of addiction.

(d) Mallinckrodt Misleadingly Told Health Care Providers that Patients Exhibiting Signs of Addiction Were Likely “Pseudoaddicted” and in Need of Additional Opioids to Treat Pain

557. As discussed above, pseudoaddiction is not supported by substantial evidence.

558. Notwithstanding the lack of substantial evidence to support the concept of pseudoaddiction, Mallinckrodt promoted pseudoaddiction through the CARES Alliance, in unbranded pocket cards distributed at trade shows, and in sales training materials.

559. The CARES Alliance supported by Mallinckrodt disseminated “education” and literature that recognized pseudoaddiction as a medical condition despite a lack of substantial evidence.

559.1. A June 2010 CARES Alliance Opioid Clinical Management Education Module in a slide entitled “Pseudoaddiction” taught healthcare providers “Aberrant behaviors due to undertreatment of pain” “includ[e] inappropriate drug seeking behaviors. Unlike true addiction, when pain is effectively treated [a]berrant behaviors resolve.”¹¹²⁷

559.2. The speaker’s notes in the same Education Module stated “Pseudoaddiction: Patients who are receiving an inadequate dose of opioid medications and seek more.”¹¹²⁸

¹¹²⁷ MNK-T1_0001492929 at slide 21.

¹¹²⁸ *Id.* at slide 49.

559.3. The Glossary of Terms in the Education Module similarly defined pseudoaddiction as “Patients who are receiving an inadequate dose of opioid medication and seek more pain medication to obtain relief.”¹¹²⁹

559.4. The speaker’s notes for a slide entitled “Managing Nonadherent Patients” in an April 13, 2011 CARES Alliance Education Module sponsored by Mallinckrodt similarly stated “Pseudoaddiction: Patients who are receiving an inadequate dose of opioid medications and seek more.”¹¹³⁰

559.5. The Glossary of Terms in the Education Module similarly defined pseudoaddiction as “Patients who are receiving an inadequate dose of opioid medication and seek more pain medication to obtain relief.”¹¹³¹

559.6. A CARES Alliance brochure entitled “Opioid Clinical Management Guide: A Resource for Responsible Opioid Prescribing and Use” instructed “[s]ome patients may exhibit aberrant behaviors, including inappropriate drug seeking behaviors when pain is undertreated. Unlike true addiction, however, these behaviors resolve and function and quality of life increase when pain is effectively treated.”¹¹³²

559.7. The CARES Alliance also promoted *Responsible Opioid Prescribing: A Physician’s Guide* by Scott Fishman, M.D.¹¹³³ *Responsible Opioid Prescribing* taught healthcare providers to “[b]e aware of the distinction between *pseudoaddiction* and

¹¹²⁹ *Id.* at slide 63. An August 10, 2010 “Train-the-Trainer” Exalgo REMS & CARES Alliance Education Module for Steven Passik, PhD, similarly instructed that “[p]seudoaddiction” was an “[a]berrant behavior[] due to undertreatment of pain” and that “unlike true addiction, when pain is effectively treated [a]berrant behaviors resolve” and defined pseudoaddiction as “[p]atients who are receiving an inadequate dose of opioid medication and seek more pain medication to obtain pain relief.” MNK-T1_0001490570 at slides 23, 65.

¹¹³⁰ MNK-T1_0001492936 at slide 20.

¹¹³¹ *Id.* at slide 73.

¹¹³² MNK-T1_0007097450 at 5.

¹¹³³ Kevin Webb Dep. Tr. Ex. 15 at 7 (MNK-T1_0001493093 at 4).

addiction. Patients who are receiving an inadequate dose of opioid medication often ‘seek’ more pain medications to obtain pain relief. This is called pseudoaddiction because healthcare practitioners can mistake it for the drug-seeking behavior of addiction . . .

Some common signs of pseudoaddiction resulting from inadequate analgesia are:

Requesting analgesics by name, Demanding or manipulative behavior, Clock watching, Taking opioid drugs for an extended period, Obtaining opioid drugs from more than one physician [] and Hoarding opioids.”¹¹³⁴

560. In addition, Mallinckrodt distributed the American Society of Pain Educators Pocket Guides at trade shows¹¹³⁵ and paid to have Exalgo in the drug table of the Guides.¹¹³⁶ The pocket cards told healthcare providers that “drug- seeking behavior focused on pain relief, due to undertreatment of pain” was “[b]ehavior [that] normalizes with adequate analgesia.”¹¹³⁷

561. Mallinckrodt likewise trained its sales force on the concept. “Module 7” on “Misuse, Abuse, Diversion and Addiction” stated “[t]his module begins with definitions of the common terminology associated with opioid use . . . Patients with pain who are prescribed opioid therapy may exhibit a range of behavioral responses” including “pseudoaddiction” defined as “result[ing] from inadequate analgesia (not addiction), yet patient display symptoms that can mimic addiction.”¹¹³⁸

¹¹³⁴ MNK-T1_0001072077 at page 62 of *Responsible of Opioid Prescribing: A Physician’s Guide*. The book added that “these same behavioral signs can indicate addiction. One way to discriminate between the two is to observe as closely as possible the functional consequences of opioid use. Whereas pseudoaddiction resolves when the patient obtains adequate analgesia, addictive behavior does not. Consultation with an addiction medicine specialist or psychiatrist may be necessary at the point when addiction becomes a concern.”

¹¹³⁵ MNK-T1_0002159712.

¹¹³⁶ MNK-T1_0001786857.

¹¹³⁷ MNK-T1_0001786865 at 9.

¹¹³⁸ MNK-T1_0007169529 at 23.

562. In my opinion, Mallinckrodt misleadingly told healthcare providers and trained its sales force that patients exhibiting signs of addiction were likely “pseudoaddicted” and in need of additional opioids to treat pain.

C. Xartemis XR

563. Xartemis XR is an extended-release combination of oxycodone and acetaminophen.

564. Mallinckrodt received FDA approval for Xartemis XR Extended Release Tablets 7.5/325 mg for “the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate” on March 11, 2014.¹¹³⁹

565. From 2014 to 2017, Mallinckrodt’s sales of Xartemis XR exceeded \$13.1 million dollars.¹¹⁴⁰

1. Mallinckrodt’s Marketing Strategy for Xartemis

566. According to the preapproval Launch “Playbook” for Xartemis, Mallinckrodt’s “[p]ositioning statement” for Xartemis XR was “Superior Percocet”¹¹⁴¹ as the first long acting oxycodone/acetaminophen product for acute pain patients. The Playbook elaborated that the positioning statement would be directed to “[health care providers] who routinely prescribe Percocet.” This positioning statement would be communicated to health care providers with the message that Xartemis XR “is the first and only controlled-release oxycodone/APAP product” that “provides fast-acting and long-last pain relief without concerns about abuse” because “it’s formulated with unique physical properties that yield an improved pharmacokinetic profile.”¹¹⁴²

¹¹³⁹ MNK-T1_0002446841 at 1, MNK-T1_0001957485.

¹¹⁴⁰ See Ex. 5 to Mallinckrodt’s Supplemental Responses and Objections to Interrogatories Nos. 1, 5, 7, 8, 9, 16, 21, 22, 23, 27, 30, 31, 32, 33, and 35, dated Jan. 30, 2019.

¹¹⁴¹ MNK-T1_0000257748 at 19.

¹¹⁴² MNK-T10000257748 at 19.

567. Mallinckrodt's "Playbook" for Xartemis XR stated this message was provided to prescribers so that "they can confidently provide a superior treatment that is more responsible to patients and society."¹¹⁴³

568. In preparing to launch Xartemis XR, Mallinckrodt's "[m]ission" was to "[e]stablish market appreciation and need for abuse-resistant technology for the treatment of acute pain" and "[e]stablish XARTEMIS as a new treatment, well-know drug combination with broad clinical utility," including "Abuse Resistant Technology [that] provides HCP greater comfort to prescribe due to advantages compared to IR OC/APA when tampered/abuse."¹¹⁴⁴

569. According to a draft marketing presentation titled "GO TIME" by Mallinckrodt's Product Director for Xartemis XR, Michael Wessler, "[s]uccessful commercialization of XARTEMIS XR is reliant upon challenging currently engrained prescribing habits,"¹¹⁴⁵ i.e. that the treatment of acute pain warranted a long-acting opioid product with abuse-deterrent properties.

570. Prior to the approval of Xartemis XR, Mallinckrodt utilized the CARES Alliaceto redefine Mallinckrodt as responsible company developing ADT products in an era of increasing opioid abuse.¹¹⁴⁶

571. In an October 16, 2013 presentation, an "[a]dvocacy initiative" of Mallinckrodt included "[r]ebranding/expanding CARES Alliance ... as a vehicle to amplify the collaborative efforts of Mallinckrodt and its advocacy partners to address the societal burden of the unintended

¹¹⁴³ MNK-T1_0000257748 at 19. The Xartemis XR Launch Playbook also identified "[c]ritical success factors" for the launch of Xartemis including "[g]et the physicians to rethink 15mg of Oxy in one dose," "[e]levate the unmet need(s) in the acute pain space," "[m]aximize touch points with high-potential targets through appropriate promotional mix" and "[e]mploy tactics to achieve greatest ROI." *Id.* at 7.

¹¹⁴⁴ MNK-T1_0000230267 at 2.

¹¹⁴⁵ MNK-T1_0000143151 at 5.

¹¹⁴⁶ See MNK-T1_0000225603 at 1.

consequences of prescription opioid abuse, misuse, and diversion.”¹¹⁴⁷ In addition, another initiative included in this presentation included “[l]everage C.A.R.E.S. to proactively define Mallinckrodt’s corporate reputation ... to bring market awareness to Mallinckrodt’s efforts as a responsible company in the area of opioid management.”¹¹⁴⁸

2. Mallinckrodt Misleadingly Marketed Xartemis as Having a Lower Potential for Abuse as Compared to Other Opioid Products.

572. In its NDA submission for Xartemis XR, Mallinckrodt maintained that Xartemis XR had abuse deterred properties,¹¹⁴⁹ and sought labeling that identified Xartemis XR as having abuse deterrent properties.

573. In 2013, FDA determined that Mallinckrodt lacked sufficient clinical data to support the abuse deterrent properties of Xartemis XR.

573.1. In the Risk Assessment and Risk Mitigation Review of Xartemis XR dated October 17, 2013, FDA noted that “[t]he only product characteristic difference between the immediate-release product and Xartemis XR is duration of action.”¹¹⁵⁰

573.2. A few months later on November 7, 2013, the Cross Discipline Team Leader issued her memorandum, stating that ADT labeling would not be permitted:

A CDTL memo was filed in FARRTS on November 7, 2013, that reviewed the submission for Xartemis CR including summary of the Controlled Substance Staff (CSS) review of the in vivo and in vitro data submitted in the original NDA submission by the Applicant to support abuse deterrent (AD) properties of Xartemis CR and labeling language regarding these properties. The conclusion reached at that time was that the Applicant had adequately demonstrated safety and efficacy of Xartemis XR for the treatment of acute pain, however the in vitro and in

¹¹⁴⁷ MNK-T1_0000222031 at 6.

¹¹⁴⁸ MNK-T1_0000222031 at 6.

¹¹⁴⁹ MNK-T1_0000000313 at 1.

¹¹⁵⁰ FDA Risk Assessment and Risk Mitigation Review at 3, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204031Orig1s000RiskR.pdf

vivo data submitted with the NDA were not sufficient to support the abuse deterrent properties or labeling for Xartemis XR, as determined by CSS.¹¹⁵¹

574. Despite not receiving FDA approval to market Xartemis XR as having abuse deterrent properties, Mallinckrodt promoted Xartemis XR as having reduce abuse potential as compared to other opioids.

574.1. For example, in a Mallinckrodt media training document, Mallinckrodt acknowledged that FDA had denied its request for abuse deterrent labeling for Xartemis ER but nonetheless promoted various aspects of its abuse-deterrent technology, stating:

Q2. Can XARTEMIS XR be easily crushed?

A2. XARTEMIS XR can be crushed, but becomes a difficult-to-manage powder when it interacts with any liquids. Due to these product properties, in in vitro studies crushed XARTEMIS XR became a stiff, unmanageable gel when mixed with small amounts of water.

If asked about Zohydro:

Zohydro is formulated as a capsule. Since we do not have access to their formulation data, we cannot comment on this.

Q3. Does XARTEMIS XR have abuse-deterrence data that the FDA did not recognize?

A3. While the approved label for XARTEMIS XR does not include abuse-deterrent language, Mallinckrodt conducted extensive lab testing and a Human Abuse Liability (HAL) study with XARTEMIS XR. Data from this study were presented in scientific presentations at PAINWeek, September 4-7, 2013. Mallinckrodt will continue working closely with the FDA to develop more data to characterize abuse-deterrence features of XARTEMIS XR and other products utilizing this technology platform. Mallinckrodt is conducting additional studies and plans to provide additional data by the end of the year.

Should there be a FN to MNK-T1_0000102166?

1.1. In addition, Mallinckrodt sales representatives were provided with a sales aid containing a chart titled “less drug high with tampered Xartemis – study subjects reported less drug high with crushed vs. intact Xartemis.”¹¹⁵²

¹¹⁵¹ FDA Cross Discipline Team Leader Mem. at 2, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204031Orig1s000CrossR.pdf

¹¹⁵² MNK-T1_0000122250 at 4.

1.2. In this same aid, Mallinckrodt stated that “[l]ess drug high with Xartemis – study subjects reported less drug high with Xartemis vs Percocet” and “Xartemis is the only agent to meet all 3 endpoints assessing abuse potential – intact Xartemis produced subjective responses on scales of drug high, drug liking, and good drug effects that were significantly less than intact Percocet at an equivalent dose.”¹¹⁵³

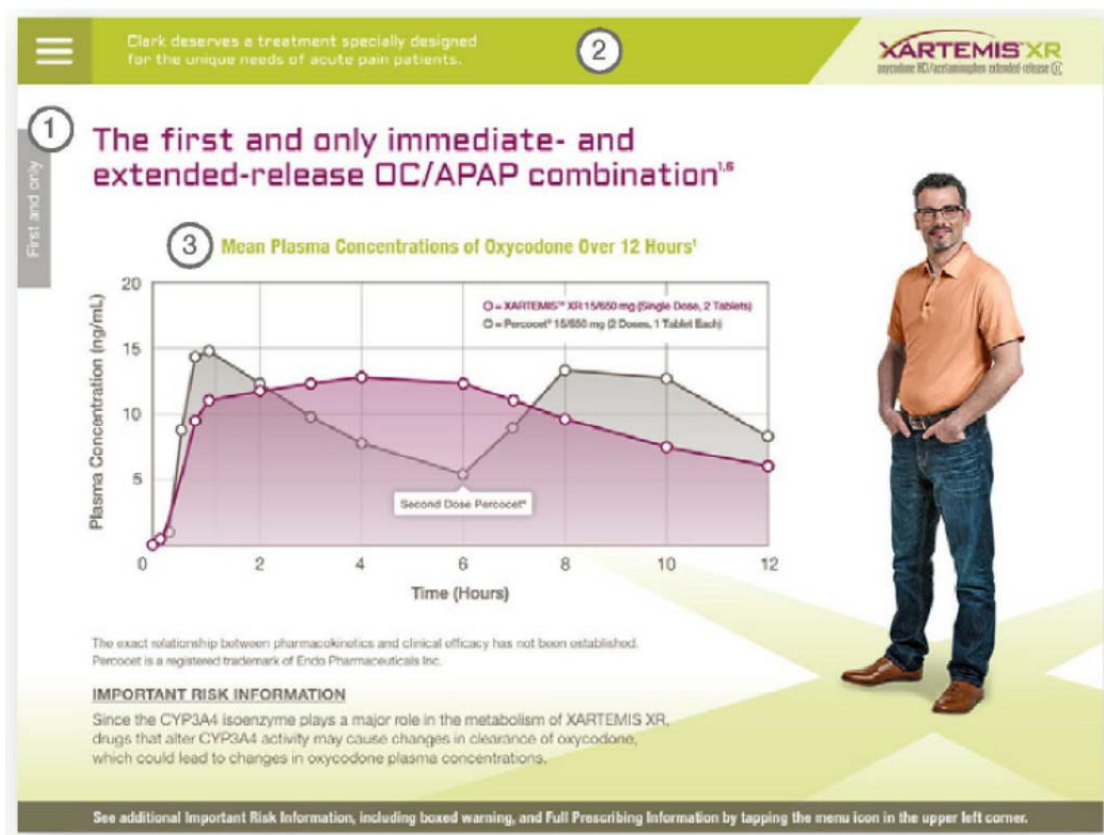
2. Just as with Exalgo, and similar to the strategy employed by Purdue in falsely marketing OxyContin as having reduced abuse potential, Mallinckrodt’s marketing highlighted the “fewer peaks and troughs” of Xartemis ER as compared to other opioid products.

2.1. For example, in the following promotional chart shown healthcare providers, Mallinckrodt instructed its sales representatives “[t]o detail this screen, you might say... The graph shows Xartemis XR maintaining plasma concentrations with fewer peaks and troughs than Percocet over 12 hours. It also demonstrates a more prolonged release versus Percocet.”

¹¹⁵³ MNK-T1_0000122250 at 5, 7. The aid likewise claimed that Xartemis was “formulated” to be “less attractive for abuse”—a claim FDA specifically rejected.

Xartemis is formulated to be less attractive for abuse” and “when ground with mortar and pestle, the percentage of release of oxycodone over the first hour was reduced with Xartemis compared to intact tablets” and “when crushed and exposed to moisture, Xartemis forms a viscous hydrogel that resists passage through a needle.”

Id. at 9.



574.2. In another sales aid, sales representatives were told “controlled release inhibits drug high with Xartemis – after a rapid initial rise, intact Xartemis yielded a lower rate of rise of oxycodone plasma concentrations than equivalent doses of intact Percocet” and “when crushed and swallowed, Xartemis yielded lower rate of rise of oxycodone plasma concentrations than intact Xartemis and intact or crushed Percocet.”¹¹⁵⁴

575. In marketing Xartemis XR, Mallinckrodt encouraged “aggressive” promotion by its sales force.

575.1. On May 19, 2014, several months after the launch of Xartemis, Hugh M. O’Neill, Mallinckrodt’s President of Specialty Pharmaceuticals, stated in an email to Stacy A. Chick, Mallinckrodt’s Vice President of Specialty Sales, “I would also like to take our highest performing 10% of reps and bring them together on a weekend to turn

¹¹⁵⁴ MNK-T1_0000122250 at 8.

them loose on the organization and the non-prescribing physicians . . . The bottom line is [] one common goal—GENERATE Prescriptions. Everything else that is not generating prescriptions should become a secondary priority.”¹¹⁵⁵

575.2. Mallinckrodt recognized “top performing [sales] representatives” with “incentive program[s].”¹¹⁵⁶ For example, the “Fast Start Challenge Reward Trip” rewarded “top performing representatives” with an opportunity to “have two minutes to run through a warehouse” and “grab things off the shelves in [a] warehouse that was set up by the vendor and they could have that . . . as a gift to themselves.” The items included “[e]lectronic items, games, toys, a myriad of things.”¹¹⁵⁷

575.3. An August 15, 2013 email from Krishnan Paranjothi, Mallinckrodt Senior District Sales Manager, Kansas City, District to Jason Daharsh and other sales representatives counseled “You only have 1 responsibility, SELL BABY SELL!”¹¹⁵⁸

576. In my opinion, Mallinckrodt falsely marketed Xartemis as having a lower potential for abuse as compared to other opioid products.

XI. THE OPIOID MANUFACTURERS’ SUPPORT FOR AND INVOLVEMENT WITH PAIN ADVOCACY, PROFESSIONAL MEDICAL AND TRADE GROUP ORGANIZATIONS, EXPANDED THE USE OF OPIOIDS AND INCREASED THE RISK OF ABUSE

577. The opioid manufacturer addressed in this report, as briefly described in the above sections, provided support to pain advocacy, professional medical organizations, and trade group

¹¹⁵⁵ MNK-T1_0000545754 at 4; *see also* MNK-T1_0000545281 at 3; MNK-T1_0004158296.

¹¹⁵⁶ Ron Wickline Dep. Tr. 121:15-124:15; Mallinckrodt sales representatives were paid a “base salary” and received a “variable incentive performance-based component of their compensation.” Stacey Chick Dep. Tr. 170:19-171:22. The incentive performance-based component of their compensation was based on “number of prescriptions” and “potential in the territory.” *Id.* at 171:23-172:1, 172:4-7.

¹¹⁵⁷ *Id.* at 123:23-124:15

¹¹⁵⁸ MNK-T1_0002803531 at 1.

organizations, and were involved in varying ways in the development and dissemination of guidelines and other promotional materials published by these groups that served the common purpose of expanding the use of opioids.

578. Through these guidelines and other materials, the opioid manufacturers contributed to altering the standard of care for the treatment of pain by encouraging healthcare providers to view pain as a “fifth vital sign” that demanded aggressive treatment with opioids.

579. In addition, these guidelines and materials echoed certain statements made by the manufacturers regarding the risks and benefits of opioids that lacked substantial supporting evidence and were false and misleading.

580. As discussed below, the opioid manufacturers’ support for and involvement with pain advocacy, professional medical and trade group organizations, expanded the use of opioids and increased the risk of addiction abuse, overdose and death.

A. American Pain Society

581. According to its bylaws, the American Pain Society (“APS”) is a “multidisciplinary community that brings together a diverse group of professionals to increase the knowledge of pain and transform public policy and clinical practice.”¹¹⁵⁹

582. Since at least 1995, APS has received funding from several opioid manufacturers.

582.1. Between 1997 and 2012, Purdue paid the APS more than \$3,000,000.00.¹¹⁶⁰

582.2. Between 1997 and 2012, Janssen paid the APS more than \$1,700,000.00.¹¹⁶¹

¹¹⁵⁹ See <http://americanpainsociety.org/uploads/about/APS%20Bylaws%20revised%2001.21.2019.pdf>; JAN-MS-00409411.

¹¹⁶⁰ SFC00000001.

582.3. Between 1998 and 2012, Endo paid the APS \$4,468,253.10.¹¹⁶²

582.4. Between 2009 and 2013, the APS was paid \$278,000.00 by Covidien and \$218,000.00 by Teva.¹¹⁶³

583. APS has maintained a “Corporate Council” program that is sponsored by opioid manufacturers. Through this program, APS “connects” members of this “Corporate Council” to “multidisciplinary leaders in the science of pain.” Members of APS’s Corporate Council include Endo, Actavis, Mallinckrodt, Purdue, and Janssen.¹¹⁶⁴

584. In addition, APS has maintained an “APS Clinical Guidelines Program” funded by opioid manufacturers. In exchange for sponsorship, opioid manufacturers are permitted “to sit on the founding members’ guideline committee and provide input into topics for guideline development, as well as suggestions of clinicians for participation in the guidelines development process, methods of dissemination/adoption, etc.”¹¹⁶⁵ Members of APS’s Guidelines Program include Purdue, Endo, and Janssen.¹¹⁶⁶

585. As described below, APS has published newsbulletins and guidelines that were authored by individuals with direct ties to opioid manufacturers and which contained the same misleading statements regarding the benefits and risks of opioids as those used by opioid manufacturers in their branded promotion.

¹¹⁶¹ JJ-SFC-00000001.

¹¹⁶² ENDO-OR-CID-00754369 at 30.

¹¹⁶³ APS-MDL00000001.

¹¹⁶⁴ TEVA_MDL_A_00499668 at 24; *see also* U.S. Senate Homeland Security & Governmental Affairs Committee, Minority Staff Report (2018), Fueling an Epidemic (Report Two) – Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups at 13.

¹¹⁶⁵ ENDO-OPIOID_MDL-06234663.

¹¹⁶⁶ PKY181215749 at 14; PKY181775488.

1. APS/AAPM Guideline – The Use of Opioids for the Treatment of Chronic Pain

586. In 1997, in a joint publication with the American Academy of Pain Medicine (“AAPM”), APS and AAPM published a guideline titled “The Use of Opioids for the Treatment of Chronic Pain,”¹¹⁶⁷ containing the following misleading statements regarding opioids:

586.1. “Studies indicate that the de novo development of addiction when opioids are used for the relief of pain is low.”¹¹⁶⁸

586.2. “[E]xperience has shown that known addicts can benefit from the carefully supervised, judicious use of opioids for the treatment of pain due to cancer, surgery, or recurrent painful illnesses[.]”¹¹⁶⁹

586.3. “It is now accepted by practitioners of the specialty of pain medicine that respiratory depression induced by opioids tends to be a short-lived phenomenon, generally occurs only in the opioid-naive patient, and is antagonized by pain. Therefore, withholding the appropriate use of opioids from a patient who is experiencing pain on the basis of respiratory concerns is unwarranted.”¹¹⁷⁰

586.4. “Furthermore, for most opioids, there does not appear to be an arbitrary upper dosage limit, as was previously thought.”¹¹⁷¹

586.5. “The undertreatment of pain in today’s society is not justified. This joint consensus statement has been produced pursuant to the missions of both organizations, to

¹¹⁶⁷ PPLPC051000030818 at 2.

¹¹⁶⁸ PPLPC051000030818 at 2.

¹¹⁶⁹ PPLPC051000030818 at 2.

¹¹⁷⁰ PPLPC051000030818 at 2.

¹¹⁷¹ PPLPC051000030818 at 2.

help foster a practice environment in which opioids may be used appropriately to reduce needless suffering from pain.”¹¹⁷²

587. The authors of this guideline included those with ties to opioid manufacturers, including: J. David Haddox, M.D.,¹¹⁷³ David Joranson,¹¹⁷⁴ Richard Payne, M.D.,¹¹⁷⁵ and Richard Portenoy, M.D.¹¹⁷⁶

588. In the same year that this APS guideline was published, the following manufacturers made the following payments to APS:

588.1. For example, in 1997, Purdue reportedly paid \$48,501 and Janssen paid \$146,245 to the APS.¹¹⁷⁷

588.2. Likewise, Purdue paid \$36,800 and Janssen paid \$43,500 to the AAPM in 1997.¹¹⁷⁸

589. This guideline was used by opioid manufacturers in promoting their opioid products and opioids in general.¹¹⁷⁹

¹¹⁷² PPLPC051000030818 at 4.

¹¹⁷³ At the time, Dr. Haddox was a paid speaker for Purdue. *See, e.g.*, PKY180955294 at 1. He was subsequently employed by Purdue as the Vice President of Risk Management and Policy. J. David Haddox Depo. Tr. 57:7-18.

¹¹⁷⁴ Mr. Joranson is the former director of the University of Wisconsin Pain & Policy Study Group, which was funded by the opioid manufacturers. ENDO-OPIOID_MDL-00658641 at 2-3. The Pain and Policy Study Group also received payments from the manufacturers. *See, e.g.* ENDO-OR-CID-00754369 at 30, SFC00000001.

¹¹⁷⁵ At the time, Dr. Payne was a paid speaker for Purdue. *See, e.g.*, PKY180256893 at 1, PKY180256892 at 1, PKY180783690 at 1.

¹¹⁷⁶ At the time, Dr. Portenoy was a paid speaker for Purdue. *See, e.g.*, PKY180357269 at 1.

¹¹⁷⁷ 2012.06.08 Purdue Summary of Payments by Name and Year SFC00000001; J&J Janssen SFC 2012 Submission JAN00000001.

¹¹⁷⁸ 2012.06.08 Purdue Summary of Payments by Name and Year SFC00000001; J&J Janssen SFC 2012 Submission JAN00000001.

¹¹⁷⁹ *See, e.g.*, PKY181199494 at 17, 25; PKY181137481 at 8; ALLERGAN_MDL_02158487 at 1; ABT-MDL-KY-0009437 at 54; ENDO-OPIOID_MDL-05967764 at 1.

2. APS/AAPM/ASAM – Definitions Related to the Use of Opioids for the Treatment of Pain

590. In 2001, APS developed consensus “Definitions Related to the Use of Opioids for the Treatment of Pain” in coordination with AAPM and the American Society of Addiction Medicine (“ASAM”), containing the following misleading statement concerning pseudoaddiction: “An individual's behaviors that may suggest addiction sometimes are simply a reflection of unrelieved pain or other problems unrelated to addiction.”¹¹⁸⁰

591. In the same year that this 2001 APS/AAPM/ASAM guideline was published, the following manufacturers made the following payments to APS/AAPM/ASAM:

591.1. For example, in 2001, Purdue reportedly paid \$211,211, Janssen paid approximately \$159,000, and Endo paid \$132,400 to APS.¹¹⁸¹

591.2. Likewise, Purdue paid \$80,273, Janssen paid \$66,764, and Endo paid \$22,000 to AAPM in 2001.¹¹⁸²

591.3. That same year, Endo paid \$10,000 to ASAM.¹¹⁸³

592. It appears that Endo may have influenced the final product,¹¹⁸⁴ and that Purdue was heavily involved in the development of these definitions. Dr. Haddox noted, “Purdue has been at the forefront of efforts to promote the proper therapeutic use of opioid analgesics, including funding the very first meeting of the AAPM/APS/ASAM

¹¹⁸⁰ PDD1502210202 at 254.

¹¹⁸¹ See SFC00000001; END00000002; JAN00000001.

¹¹⁸² END00000002; JAN00000001.

¹¹⁸³ ENDO-OPIOID_MDL-06234588; JAN00000001.

¹¹⁸⁴ See END00211516.

leadership (when I was president of AAPM) to begin the collaboration that eventually led to the Consensus statement on definitions of pain and addiction.”¹¹⁸⁵

593. This guideline was used by opioid manufacturers in promoting their opioid products and opioids in general.¹¹⁸⁶

3. APS Arthritis Guidelines

594. In 2002, the APS issued “Guidelines for the Management of Arthritis Pain,” containing the following misleading statements:

594.1. “The prevalence of addiction among patients with pain who do not have a previously existing substance abuse disorder is low.”¹¹⁸⁷

594.2. “Weissman and Haddox (1989) noted that patients who are given doses of opioids that are inadequate to relieve their pain or whose opioid dose is discontinued abruptly or tapered too rapidly may develop characteristics that resemble addiction, which they termed iatrogenic ‘pseudoaddiction.’”¹¹⁸⁸

594.3. “Tolerance to analgesia is uncommon once pain relief has been achieved and there is no progression of disease.”¹¹⁸⁹

594.4. “Opioids should be used for patients with OA and RA when other medications and nonpharmacologic interventions produce inadequate pain relief and the patient's quality of life is affected by the pain.”¹¹⁹⁰

¹¹⁸⁵ PPLP003477086 at 24.

¹¹⁸⁶ See, e.g., END00212229; ENDO-OPIOID MDL-01997737; ENDO-OPIOID_MDL-02939611 at 68; END00212229; ABT-MDL-KY-0009437 at 54.

¹¹⁸⁷ PKY181215749 at 95.

¹¹⁸⁸ PKY181215749 at 95.

¹¹⁸⁹ PKY181215749 at 96.

¹¹⁹⁰ PKY181215749 at 97.

594.5. “Extensive experience and evidence in the management of chronic malignant pain supports the use of long-acting opioids to improve patient adherence, minimize medication level peaks and valleys, and minimize side effects. These advantages also appear to apply to the use of long-acting opioids in the management of arthritis pain, but the cost-effectiveness of the advantages has not been shown.”¹¹⁹¹

594.6. “The limited study data on effective doses of opioids for OA pain demonstrate efficacy at relatively low doses. Both immediate release and controlled release forms have been effective.”¹¹⁹²

595. The authors of this guideline included several with ties to opioid manufacturers, including Arthur G. Lipman, M.D.,¹¹⁹³ Margaret Caudill-Slosberg, M.D.,¹¹⁹⁴ and April Hazard Vallerand, Ph.D., R.N.¹¹⁹⁵

596. Opioid manufacturers funded the “APS Guidelines Program,” which the APS used to fund its consultants.”¹¹⁹⁶

597. This guideline was used by opioid manufacturers in promoting their opioid products and opioids in general.¹¹⁹⁷

¹¹⁹¹ PKY181215749 at 98.

¹¹⁹² PKY181215749 at 102. When Purdue had concerns about the content of APS materials, it reached out to KOLS involved in the development of the materials to confirm a favorable result for Purdue. For example, when Purdue’s Sally Riddle voiced her worries about the content of the APS Arthritis Guidelines, she communicated these to Harry Lazarus, who then spoke with the chair of the Guidelines, Art Lipman. After speaking with Dr. Lipman, Harry reported back to Sally “I don’t think you will be disappointed with the guidelines.” PPLPC009000006145; *see also* E513_00090393.

¹¹⁹³ Dr. Lipman was a consultant and paid speaker for Endo and Purdue. *See* PKY181215749 at 15.

¹¹⁹⁴ Dr. Caudill-Slosberg was a paid speaker for Purdue. *See* PKY181215749 at 15.

¹¹⁹⁵ Dr. Vallerand was a paid speaker for Purdue and Janssen. *See* PKY181215749 at 15.

¹¹⁹⁶ PKY181215749 at 15.

¹¹⁹⁷ *See, e.g.*, PPLPC012000051510 at 8, PPLPC012000051508, E01_00013311 at 2, PPLP003281201, PPLP012000063578; *see also* APS-MDL00000061 at APS-MDL00000062 (APS Arthritis Guidelines Total Distribution between 2002 and 2007: 193,308); PKY181947933 at 2.

B. American Academy of Pain Medicine

598. According to the mission statement of the American Academy of Pain Medicine (“AAPM”), its purpose is to “provide for quality care to patients suffering with pain, through education and training of physicians, and through the advancement of specialty of Pain Medicine.”¹¹⁹⁸

599. The AAPM received millions of dollars in funding from opioid manufacturers.

599.1. Between 1997 and 2012, Purdue provided more than \$2,000,000.00 in funding to the AAPM,¹¹⁹⁹ and from 2012 and 2017, AAPM received an additional \$700,000.00 from Purdue.¹²⁰⁰

599.2. Between 1997 and 2011, Janssen provided more than \$560,000.00. in funding to the AAP,¹²⁰¹ and from 2012 to 2017, Janssen funded the AAPM with an additional \$83,000.00.¹²⁰²

599.3. From 2010 to 2016, Mallinckrodt provided at least \$239,000.00 in funding to the AAPM.¹²⁰³

¹¹⁹⁸ JAN-MS-00723779.

¹¹⁹⁹ SFC00000001.

¹²⁰⁰ Fueling an Epidemic: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups. U.S. Senate Homeland Security & Governmental Affairs Committee, Ranking Member’s Office, PPLPC031001561047 at 5. Also available at <https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf>.

¹²⁰¹ JJ-SFC-00000001.

¹²⁰² Fueling an Epidemic: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups. U.S. Senate Homeland Security & Governmental Affairs Committee, Ranking Member’s Office, PPLPC031001561047 at 5. Also available at <https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf>.

¹²⁰³ CHI_000441993 at 18.

600. As noted in the section above pertaining to the American Pain Society (“APS”), AAPM and APS issued a joint guideline in 1997 that contained misleading statements regarding the safety of opioids.¹²⁰⁴

601. In addition to these guidelines, AAPM provided continuing medical education that was coordinated, at least in part, by opioid manufacturers such as Purdue. For example, an April 2000 email from Purdue’s Robin Hogen described Purdue’s relationship with Dr. Barry Cole, who would later become AAPM’s Executive Director:

[Dr.] Barry [Cole] is now on the road five days a week for Purdue – and seems very happy. He believes he can be more helpful to the Company by remaining a third party – unencumbered by FDA guidelines for what he can say about our products or the class of drugs. By flying under the umbrella of American Academy of Pain Management, he has tremendous credibility and cannot be discounted as a company flak.¹²⁰⁵

602. Similarly, in a May 2001 email exchange involving the AAPM’s Dr. Cole and Purdue’s Dr. Reder, Dr. Cole offered to “provide a written statement for Purdue’s support” and

¹²⁰⁴ AAPM also made misleading statements concerning the risk of addiction in other promotional materials. For example, in a 2005 Question and Answer session with the president of the American Academy of Pain Medicine, Dr. Scott Fishman gave the following misleading statements:

We know that the risks of addiction are there, but they are small and can be managed.....many have argued that if we try in our zeal to minimize the risk to avoid drugs that are addictive, we often wind up using drugs that may be even more toxic, such as NSAIDs or potentially, in some patients, COX-2 inhibitors.

PPLPC0128341 at 3. Likewise, in a 2011 “Interactive Exploration of Integrated Opioid Therapy in Chronic Pain” presentation by AAPM, the following misleading statements were made:

Some long-acting opioids help maintain steady blood serum blood levels, help patients sleep through the night, and eliminate the need for frequent dosing” and that “the less frequent administration may discourage binge behavior in patients with risks for misuse.

MNK-T1_0000984477 at 16.

¹²⁰⁵ PDD8801104393. *See also* PPLPC029000042442 at 2. In this May 2001 email, Dr. Barry Cole wrote the following to Purdue’s Dr. Reder:

Dr. Reder, Thought you’d like to see these items before next weeks meetings in CT.[...] I am attaching some articles and letters from the Cleveland Free Times....all very supportive of OxyContin and calling into question what may be entirely manufactured news. I have spoken with the reporter 3 times. He has asking all of the right questions about the OxyContin “scare.”

Id.

noted that he was “happy to prepare something as an individual or in some official capacity with the American Academy of Pain Management” for the “FDA Advisory Committee meeting in Maryland on June 14/15,” since in Dr. Cole’s opinion “this is all just ‘too much about nothing.’”¹²⁰⁶

C. American Pain Foundation

603. Founded in 1997, the American Pain Foundation (“APF”) described itself as “the nation’s leading independent nonprofit organization serving people with pain.”

604. APF ceased operating in 2012 following congressional questioning about its ties to the pharmaceutical industry, including opioid manufacturers.

605. APF received millions of dollars in funding from opioid manufacturers.

605.1. Between 1999 and 2012, Purdue provided more than \$3,600,000.00 in funding to APF.¹²⁰⁷

605.2. Mallinckrodt contributed a total of \$97,000 in funding to the APF.¹²⁰⁸

605.3. Between 1997 and 2012, Janssen funded APF with more than \$600,000.00.¹²⁰⁹

605.4. Between 1999 and 2012, Endo provided at least \$5,941,671.40 in funding to the APF.¹²¹⁰

¹²⁰⁶ PPLPC029000042442 at 1.

¹²⁰⁷ SFC00000001; *see also* 2001 APF Highlights.(CHI_000406606 at 55) (noting Purdue as its largest funder and also identifying Abbott, Anesta, Bristol-Myers Squibb, Cephalon, Janssen, Knoll, Ligand, McNeil Consumer, Medtronic, Novartis, Ortho-Biotech, Pharmacia, Pfizer, Roxane and Warner Lambert at part of their “broad corporate support.”)

¹²⁰⁸ MNK-T1_0008005740.

¹²⁰⁹ JJ-SFC-00000001.

¹²¹⁰ END00041232 at 8.

606. In exchange for funding APF, opioid manufacturers expected and received inclusion in APF decision making.

606.1. For example, in an August 5, 2000 email from Purdue's Robin Hogen to Dr. David Haddox concerning funding to APF, Hogen stated, "[i]f they want our bucks (and they honestly cannot survive without industry support) they are going to have to learn to live with 'industry' reps on their board. I don't think they can expect huge grants without some say in governance."¹²¹¹

606.2. By at least 2001, APF's Board included members with ties to opioid manufacturers, including Dr. Richard Campbell, a paid consultant for Purdue,¹²¹² and Dr. Richard Portenoy, a paid consultant and speaker for Purdue and Janssen.¹²¹³

607. APF has published promotional materials that contained the same misleading statements regarding the benefits and risks of opioids as those used by opioid manufacturers in their branded promotion.

607.1. In 2000, APF published a "Pain Action Guide" that contained the misleading claim that addiction is rare:

Pain medications rarely cause addiction. Morphine and similar pain medications, called opioids, can be highly effective for certain conditions. Unless you have a history of substance abuse, there is little risk of addiction when these medications are properly prescribed by a doctor and taken as directed. Physical dependence - which is not addiction - may occur as a result of taking these medications if you stop taking these medications suddenly. This usually is not a problem if you go off your medications generally.¹²¹⁴

¹²¹¹ PPLPC025000012558.

¹²¹² PPLP003477687.

¹²¹³ See PKY180772092; ENDO-OPIOID_MDL-01610298; PPLPC020000005715; PDD8801291781; PKY182717470; JAN-MS-00312347.

¹²¹⁴ ABT-MDL-KY-0025968; TEVA_MDL_A_05356629.

607.2. In April 2001, APF issued a news release titled “Balancing News Stories About Opioids,” which again misleadingly claimed addiction to be rare, and further claimed without substantial evidence that opioid medications rarely produce a “high” and allow patients to return to normal lives:

Taking legal, FDA-approved opioid medications as prescribed, under the direction of a physician for pain relief, is safe and effective, and only in rare cases, leads to addiction. When properly used, these medications rarely give a ‘high’ – they give relief. And, most importantly, they allow many people to resume their normal lives.¹²¹⁵

607.3. In 2007, APF provided “messages” to be used in training patient advocates regarding the use of opioids, including the statement that “[p]ain is a national healthcare crises. It is our Nation’s hidden epidemic.” These “messages” also included the following misleading statement regarding addiction:

The public—including doctors and people with pain – often believe that opioid medications are addictive and produce euphoria. The fact is that when properly prescribed by a healthcare professional and taken as directed, these medications give relief – not a ‘high.’¹²¹⁶

607.4. In October 2007, Endo sponsored an APF event “focusing on the vital need for better pain care for members of the military and veterans” entitled “Freedom From Pain: It’s Your Right.”¹²¹⁷ Endo’s financial support for the event included the preparation of a “fact sheet.”¹²¹⁸ The fact sheet included the following statements that downplayed the risk of addiction:

“A number of concerns and misconceptions stand in the way of optimal pain management. These may include fears about”

¹²¹⁵ PKY180302903 at 107.

¹²¹⁶ PPLP004046286 at 2.

¹²¹⁷ ENDO-OPIOID_MDL-02807915 at 3; CHI_000430399.

¹²¹⁸ *Id.* at 2.

“Becoming ‘drugged up’ or addicted to pain medications, if they are prescribed;”¹²¹⁹

*“Unless someone has a past or current history of substance abuse, the chance of addiction is very low when these medications are prescribed by a doctor and taken as directed.”*¹²²⁰

607.5. APF made a similarly misleading statement regarding addiction in the 2009 book titled Exit Wounds – A Survival Guide to Pain Management for Returning Veterans and their Families: “[l]ong experience with opioids shows that people who are not predisposed to addiction are unlikely to become addicted to opioid pain medication.”¹²²¹

607.6. Likewise, in 2011, APF made the following statement regarding addiction in its “Policymaker’s Guide to Understanding Pain & Its Management”:

Under a section titled “some common misconceptions about pain” it was stated that “use of strong pain medication leads to addiction. Many people living with pain, and even some health care practitioners, falsely believe that opioid pain medicines are universally addictive. As with any medication, there are risks, but these risks can be managed when these medicines are properly prescribed and taken as directed.”¹²²²

608. In addition to promoting the misleading claim that opioids are rarely addictive, APF responded to negative media attention related to diversion and abuse of opioids.

608.1. An internal APF presentation highlighted the “Media Frenzy over OxyContin and Other Opioids” and “How APF Has Been Fighting Back.”¹²²³ The presentation highlighted the fact that the APF was involved in “educating the media” by

¹²¹⁹ ENDO-OPIOID_MDL-02807915 at 7.

¹²²⁰ *Id.* at 8.

¹²²¹ SFC00005694 at 107.

¹²²² ENDO-OPIOD_MDL-00654219 at 7.

¹²²³ CHI_000406606 at 42.

“handl[ing] over 125 calls and inquiries from national, state-wide and local media” and “educated journalist on value of opioids while dispelling myths and misconceptions.”¹²²⁴ Further, the APF stated that it had “testified before congress and FDA” and had been “vocal in new pain forum with DEA” where they “insisted on major changes to DEA’s ‘consensus statement.’”¹²²⁵ APF further stated that it “educated professionals” with presentations with titles such as “are pain patients becoming collateral damage in the war on drugs” and “recent federal actions on opioids.”¹²²⁶

608.2. Similarly, the 2001 APF Board of Director Meeting Minutes state that:

[A]s a result of a NY Times article on OxyContin abuse suggesting a link between APF and Purdue Pharma, APF developed a proactive approach to the rise in reports on the negative effects of OxyContin. APF’s media response to queries is that “opioids are one of the most effective ways to treat pain. They offer pain relief, not a ‘high’, when prescribed by a doctor and taken as directed. Opioid-related deaths are the result of ‘drug abuse.’”¹²²⁷

D. Federation of State Medical Boards

609. According to its website, the Federation of State Medical Boards (“FSMB”) is a national non-profit organization representing all 70 state medical and osteopathic boards within the United States and its territories that license and discipline allopathic and osteopathic physicians and, in some jurisdictions, other health care professionals.”¹²²⁸

610. The FSMB received funding from opioid manufacturers.

¹²²⁴ *Id.* at 43.

¹²²⁵ *Id.* at 45.

¹²²⁶ *Id.* at 48.

¹²²⁷ CHI_001260895 at 6.

¹²²⁸ <http://www.fsmb.org/about-fsmb> (last visited Mar. 22, 2019).

610.1. Between 1999 and 2007, Purdue provided at least \$904,742 in funding to the FSMB.¹²²⁹ Purdue's funding paid for copies of the FSMB Pain Model Guidelines and supported the "FSMB National Clearinghouse on Internet Prescribing," the "2003 FSMB Annual Meeting Session," the "Project to Update FSMB Guidelines for the Use of Controlled Substances in the Treatment of Pain," the "FSMB Physician Education Initiative on Safe & Effective Prescribing Practices in Pain Management," and the "distribution of Responsible Opioid Prescribing to [State Medical Boards]."¹²³⁰

610.2. Between 2000 and 2010, Endo provided at least \$369,025 in funding to the FSMB.¹²³¹ Endo's funding supported distribution of Responsible Opioid prescribing to State Medical Boards and CME Activity related to Opioid REMS.¹²³²

610.3. Teva contributed a total of \$130,000 in funding to the FSMB in donations and as a "grant to support the distribution of Responsible Opioid Prescribing to [State Medical Boards]."¹²³³

610.4. Mallinckrodt similarly contributed a total of \$100,000 in funding to the FSMB as a "grant to support the distribution Responsible Opioid Prescribing to SMBs."¹²³⁴

611. As described below, the FSMB has published newsbulletins and guidelines that contained the same misleading statements regarding the benefits and risks of opioids as those used by opioid manufacturers in their branded promotion.

¹²²⁹ SFC00000001.

¹²³⁰ FSMB_00000050 at 11-12.

¹²³¹ ENDO-OR-CID-00754369.

¹²³² FSMB_00000050 at 13.

¹²³³ FSMB_00000050 at 11-12.

¹²³⁴ *Id.*

1. FSMB Model Guidelines for the Use of Controlled Substances for the Treatment of Pain

612. In 1998, the FSMB issued the Model Guidelines for the Use of Controlled Substances for the Treatment of Pain.¹²³⁵

613. These guidelines emphasized that “[i]nadequate pain control may result from physicians’ lack of knowledge about pain management or an inadequate understanding of addiction” while at the same time downplaying the risk of addiction with the false statement that pseudoaddiction is a “[p]attern of drug-seeking behavior of pain patients who are receiving inadequate pain management that can be mistaken for addiction.”¹²³⁶

614. Purdue distributed the Model Guidelines in promotion of its opioids and opioids in general.¹²³⁷

2. Updated FSMB Policy for the Use of Controlled Substances for the Treatment of Pain

615. In 2004, the FSMB issued an update to its Model Policy for the Use of Controlled Substances for the Treatment of Pain, which again contained the following misleading statements regarding addiction: “Notwithstanding progress to date in establishing state pain policies recognizing the legitimate medical uses of opioid analgesics, there is a significant body of evidence suggesting that both acute and chronic pain continue to be undertreated . . . Circumstances that contribute to the prevalence of undertreated pain include . . . ‘misunderstanding of addiction and dependence.’” The Policy then defined pseudoaddiction as the

¹²³⁵ According to a July 23, 2002 letter from Jon A. Sale to Jody Collins, Esq., Assistant Attorney General re: Purdue Pharma, L.P. the Model Guidelines were developed “with the support of the American Academy of Pain Medicine, the American Pain Society, the American Society of Law, Medicine and Ethics, and the University of Wisconsin Pain and Policy Studies Group.” PKY181679246 at 1-2.

¹²³⁶ PPLPC002000136977 at 2.

¹²³⁷ See, e.g., PKY181696752 at 2, PKY181696752 (“Purdue began distributing the Model Guidelines to physicians in early 1999 shortly after they became available. To date, through its field force, Purdue has distributed almost 300,000 copies of the Model Guidelines.”)

“iatrogenic syndrome resulting from the misinterpretation of relief seeking behaviors as though they are drug seeking behaviors that are commonly seen with addiction.”¹²³⁸

616. Opioid manufacturers were involved in drafting this policy update.

616.1. For example, as part of Purdue’s funding of FSMB, Purdue received access to the meeting that “led to the revision of the Model Guidelines to become what is now the [2004] Model Policy, upon which Dr. Fishman’s book [Responsible Opioid Prescribing] is based.”¹²³⁹

616.2. In addition, according to a September 11, 2007 email from David Haddox, he “represented Purdue” at the “meeting that led to the revision of the Model Guidelines to become what is now the [2004] Model Policy” and “many of [his] suggestions and clarifications were accepted by the group [that] revised the Guidelines into the Policy document it is today.”¹²⁴⁰ “In addition, at Dr. Fishman’s request, [Dr. Haddox] performed a detailed review of [the] final draft and submitted the comments to him, many of which” were “accepted.”¹²⁴¹

¹²³⁸ ENDO-OPIOID_MDL-02751850 at 11. The 2004 Model Policy also told healthcare providers that “they should not fear disciplinary action from the Board for ordering, prescribing, dispensing or administering controlled substances, including opioid analgesics, for a legitimate medical purpose and in the course of professional practice . . . [t]he physician’s conduct will be evaluated to a great extent by the outcome of pain treatment, recognizing that some types of pain cannot be completely relieved, and by taking into account whether the drug used is appropriate for the diagnosis, as well as improvement in patient functioning and/or quality of life.” *Id.* at 9.

¹²³⁹ PPLP003477086 at 24.

¹²⁴⁰ *Id.*

¹²⁴¹ *Id.*

617. Members of the the 2004 Model Policy Advisory Council had financial ties to the opioid manufacturers including Dr. David Haddox,¹²⁴² June L. Dahl, Ph.D.,¹²⁴³ and Scott M. Fishman,¹²⁴⁴ M.D.

618. The model policy was used by opioid manufacturers in promoting their opioid products and opioids in general.¹²⁴⁵

3. FSMB Responsible Opioid Prescribing

619. In 2007, the FSMB published Responsible Opioid Prescribing which made the same claims as the 1998 FSMB Model Guidelines and 2004 FSMB Model Policy, including false statements regarding pseudoaddiction.¹²⁴⁶

620. Financial support from Purdue, Endo, Cephalon, and Mallinckrodt in addition to other opioid manufacturers, supported distribution of over 160,000 copies of the book to state medical boards.¹²⁴⁷

621. In addition, Mallinckrodt (and likely others) used Responsible Opioid Prescribing in promotion of its opioids and opioids in general to healthcare providers.¹²⁴⁸

622. In my opinion, opioid manufacturers' support for and involvement with pain advocacy, professional medical and trade group organizations expanded the use of opioids and increased the risk of abuse.

¹²⁴² David Haddox was Vice-President, Risk Management & Health Policy, at Purdue. J. David Haddox Depo. Tr. 57:7-18.

¹²⁴³ See, e.g., PKY180470186.

¹²⁴⁴ See, e.g., SFC00000001; ENDO-OR-CID-00754369 at 21.

¹²⁴⁵ ENDO-OR-CID-00754369 at 13;

¹²⁴⁶ ENDO-OR-CID-00754369 at 13.

¹²⁴⁷ FSMB000000050 at 10-14, 18-19.

¹²⁴⁸ MNK-T1_0000098925 (Mallinckrodt).

XII. CORRECTIVE MEASURES

623. Based on the totality of the above, it is my opinion that corrective promotion, advertising, and professional education initiatives to audiences that received the false and misleading messages discussed in this report are called for. Though not intended as an exhaustive list, examples of such corrective promotion and advertising could include the following messages:

501.1 Opioids present an unavoidable risk of addiction, overdose and death, even when used as prescribed.

501.2 Opioids should not commonly be used for chronic pain.

501.3 Opioids should be prescribed at the lowest possible dose for the shortest possible time.

624. Additional messages such as those adopted by the Truth Initiative should be used in corrective promotion.

625. In addition to corrective promotion, manufacturers should assure that no claims, including any superiority claims, about opioids are made without validation of those claims by high-quality and well-controlled clinical studies.

626. Moreover, to correct the results of past practices, in my opinion, manufacturers should not fund treatment guidelines, organizations that issue treatment guidelines, or any authors of guidelines that concern pain, opioids or addiction. Disclosure of past and present funding from manufacturers to organizations and individuals that issue or author treatment guidelines should also be made.

627. As in other corrective programs, it would also be useful to disclose historical manufacturer documents concerning opioids to the public, while still protecting personal health information.

XIII. CONCLUSIONS

1. In this report, I have provided the following opinions:
2. In my opinion, Purdue utilized promotional tactics that misbranded OxyContin as a drug that is safer and more effective than it actually is without substantial evidence.
3. In my opinion, Purdue's marketing minimized the similarities between OxyContin and morphine.
4. In my opinion, Purdue falsely marketed OxyContin as having a lower potential for abuse as compared to other opioid products.
5. In my opinion, Purdue's marketing misleadingly claimed without substantial evidence that OxyContin was less addictive than competitor opioid products.
6. In my opinion, Purdue misleadingly told health care providers that patients exhibiting signs of addiction were likely "psuedoaddicted" and in need of additional opioids to treat pain.
7. In my opinion, Purdue minimized the risks of tolerance and physical dependence that patients could experience with OxyContin.
8. In my opinion, Purdue's marketing minimized the risks of respiratory depression, addiction, and abuse associated with higher doses of OxyContin.
9. In my opinion, Purdue overstated the 12-hour analgesic benefit of OxyContin.
10. In my opinion, Purdue overstated the benefits of OxyContin with respect to sleep, work, and physical activity/leisure.
11. In my opinion, Purdue put patients at risk by developing a strategy to increase the total daily OxyContin dose without informing the public that OxyContin was not effective for 12 hours.

12. In my opinion, Purdue promoted OxyContin for indications that were broader than supported by substantial evidence and for which safety and efficacy were not established.

13. In my opinion, Purdue failed to align its promotional activities with its Risk Management Program and Risk Evaluation and Mitigation Strategies.

14. In my opinion, Endo's marketing activities understated the risks of the entire class of opioids.

15. In my opinion, by promoting higher doses of Percocet, Endo minimized the risks of respiratory depression and abuse associated with higher doses of opioids.

16. In my opinion, Endo overstated the benefits of Percocet with respect to quality of life.

17. In my opinion, Endo falsely marketed Opana ER as having lower abuse potential and as safer than other opioid products.

18. In my opinion, Endo minimized the risk of addiction associated with Opana ER and funded various pain organizations to likewise minimize the risk of addiction.

19. In my opinion, Endo falsely told healthcare providers that patients exhibiting signs of addiction could be exhibiting "pseudoaddiction" and in need of additional opioids to treat pain.

20. In my opinion, Endo promoted Opana ER as having no dose ceiling but minimized the risks associated with higher doses.

21. In my opinion, Endo overstated the benefits of Opana ER with respect to work and functionality.

22. In my opinion, Endo minimized the risk of addiction associated with Opana ER and opioids in general through its distribution of the AAPM/APS "Consensus Statement on the

Use of Opioids for the Treatment of Chronic Pain” and “A clinical guide to Opioid Analgesia” as part of the Opana ER Riskmap.

23. In my opinion, the “Professional Education Initiatives” Endo supported in the Opana ER Riskmap minimized the risk of addiction associated with opioids.

24. In my opinion, Endo marketed Opana ER as “Crush Resistant” despite FDA’s instruction otherwise.

25. In my opinion, Endo failed to take reasonable steps to protect the public health despite increasing evidence of Opana ER Reformulated abuse.

26. In my opinion, Janssen’s marketing of Duragesic broadened its indications beyond the label, and thereby expanded the use of long acting opioids and contributed to the change in the practice of medicine.

27. In my opinion, Janssen misleadingly promoted Duragesic as superior to oral opioids, especially OxyContin, without substantial evidence, and overstated its functionality benefits.

28. In my opinion, Janssen misleadingly promoted Duragesic as having no or lower abuse potential, particularly compared with OxyContin, without substantial evidence.

29. In my opinion, Janssen made misleading, unsubstantiated and shifting claims regarding the abuse potential of the reservoir v. matrix formulations of Duragesic as the sales and regulatory environment changed.

30. In my opinion, Janssen’s promotion of Duragesic understated its risks and overstated its benefits, and was false and misleading.

31. In my opinion, Janssen overstated the benefits of Nucynta’s mechanism of action, promoting it as offering increased efficacy without substantial evidence.

32. In my opinion, Janssen overstated the benefits of Nucynta's GI tolerability, making superiority claims without substantial supporting evidence.

33. In my opinion, Janssen's promotion of Nucynta misleadingly minimized the risks of abuse and addiction.

34. In my opinion, Teva marketed Actiq for indications that lacked substantial evidence to support safety.

35. In my opinion, Teva failed to comply with its risk management strategies in marketing Actiq.

36. In my opinion, Teva promoted Fentora for non-malignant pain, for which it lacked substantial evidence to support safety.

37. In my opinion, Actavis promoted Kadian for indications broader than supported by substantial evidence and for which safety and efficacy were not established.

38. In my opinion, Actavis's promotional materials overstated the benefits of Kadian with respect to patient functionality and quality of life

39. In my opinion, Actavis falsely marketed Kadian as safer and more effective than other opioid products.

40. In my opinion, Actavis falsely promoted Kadian as having no alcohol-induced dose-dumping effect and failed to take reasonable measures to correct prescriber misperceptions regarding this promotional claim.

41. In my opinion, Actavis's promotion of opioids minimized the risks of addiction and abuse.

42. In my opinion, Mallinckrodt falsely promoted Exalgo as safer than other opioid products.

43. In my opinion, Mallinckrodt's sales training misleadingly minimized the risks associated with higher doses of opioids and encouraged sales representatives to make misleading claims regarding abuse deterrence.

44. In my opinion, Mallinckrodt misleadingly minimized the risk of addiction and funded the CARES Alliance which likewise understated the risk of addiction.

45. In my opinion, Mallinckrodt misleadingly told healthcare providers and trained its sales force that patients exhibiting signs of addiction were likely "pseudoaddicted" and in need of additional opioids to treat pain.

46. In my opinion, Mallinckrodt falsely marketed Xartemis as having a lower potential for abuse as compared to other opioid products.

47. In my opinion, through the pain advocacy group guidelines and materials they helped develop and disseminate, opioid manufacturers contributed to altering the standard of care for the treatment of pain by encouraging healthcare providers to view pain as a "fifth vital sign" that demanded aggressive treatment with opioids.

48. In my opinion, opioid manufacturers' support for and involvement with pain advocacy, professional medical and trade group organizations expanded the use of opioids and increased the risk of abuse.

49. In my opinion, the promotional violations discussed above endanger public health because they encourage the use of opioids in circumstances other than those in which the drugs have been approved, overstate their benefits and minimize their risks.

50. In my opinion, because the promotional violations discussed in this report are serious, corrective promotion and medical education that disseminates truthful, non-misleading,

and complete corrective messaging about the violations discussed above to the audiences that received the violative promotion is warranted.

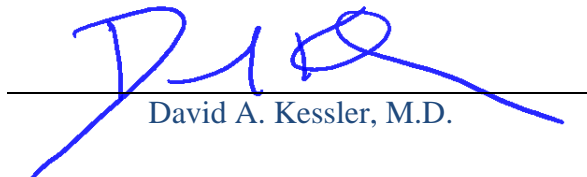
51. In my opinion, the need for corrective promotion here is supported by research that has demonstrated that similar corrective promotion can be effective in countering false and misleading statements made about prescription drug products.

52. In my opinion, manufacturers should assure that no claims, including any superiority claims, about opioids are made without validation of those claims by high quality and well controlled clinical studies.

53. In my opinion, to correct the results of past practices, manufacturers should not fund treatment guidelines, organizations that issue treatment guidelines, or any authors of guidelines that concern pain, opioids or addiction. Disclosure of past and present funding from manufacturers to organizations and individuals that issue or author treatment guidelines should also be made.

54. Based on the totality of the above, it is my opinion that the manufacturers' departures from FDA standards would be expected to (and likely did) have an affect on how healthcare providers prescribed opioids, contributing to a shift in the practice of medicine with regards to the use of opioids in the treatment of pain. This change in the practice of medicine led to an increase in opioid prescriptions, an increase of opioids in interstate commerce, and an increase in inappropriate use of opioids, all of which in turn increased the risk of opioid abuse and contributed to a public health crisis.

March 26, 2019



David A. Kessler, M.D.

APPENDIX A

DAVID A. KESSLER

1969-1973	AMHERST COLLEGE, Amherst, Massachusetts Bachelor of Arts, <i>magna cum laude</i> (B.A. Independent Scholar, 1973)
1973-1979	HARVARD MEDICAL SCHOOL, Boston, Massachusetts Doctor of Medicine (M.D. 1979)
1975-1977	UNIVERSITY OF CHICAGO LAW SCHOOL, Chicago, Illinois Doctor of Law (J.D., 1978), Harvard Law School, 1977-1978
1984-1986	NEW YORK UNIVERSITY GRADUATE SCHOOL OF BUSINESS ADMINISTRATION (Manhattanville), Purchase, New York Advanced Professional Certificate in Management

EMPLOYMENT

2003-present	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO Professor of Pediatrics, Epidemiology and Biostatistics
2003-2007	Dean, School of Medicine Vice Chancellor of Medical Affairs
1997-2003	YALE UNIVERSITY SCHOOL OF MEDICINE Dean Professor of Pediatrics, Internal Medicine, and Public Health
1990-1997	UNITED STATES FOOD AND DRUG ADMINISTRATION Commissioner (Appointed by President George H. W. Bush, Reappointed by President William J. Clinton)
1984-1990	THE HOSPITAL OF THE ALBERT EINSTEIN COLLEGE OF MEDICINE Medical Director
1986-1990	COLUMBIA UNIVERSITY Julius Silver Program in Law, Science and Technology Lecturer on Law
1982-1984	MONTEFIORE MEDICAL CENTER Special Assistant to the President
1981-1984	UNITED STATES SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES, Consultant to the Chairman

HONORARY DEGREES

1992	AMHERST COLLEGE, Amherst, Massachusetts Doctor of Science <i>honoris causa</i>
1992	GEORGE WASHINGTON UNIVERSITY, Washington, D.C. Doctor of Science <i>honoris causa</i>
1993	PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE, Philadelphia, Pennsylvania, Doctor of Science <i>honoris causa</i>
1993	DICKINSON COLLEGE OF LAW, Carlisle, Pennsylvania Doctor of Laws <i>honoris causa</i>
1995	ALBANY MEDICAL COLLEGE, Albany, New York Doctor of Science <i>honoris causa</i>
1997	NORTHEASTERN UNIVERSITY, Boston, Massachusetts Doctor of Science <i>honoris causa</i>
1998	MOUNT SINAI SCHOOL OF MEDICINE, New York, New York Doctor of Humane Letters <i>honoris causa</i>
1998	COLGATE UNIVERSITY, Hamilton, New York Doctor of Science <i>honoris causa</i>
1998	YALE UNIVERSITY, New Haven, Connecticut Master of Arts <i>privatim</i>
1999	CONNECTICUT COLLEGE, New London, Connecticut Doctor of Humane Letters <i>honoris causa</i>
2001	DICKINSON COLLEGE, Carlisle, Pennsylvania Doctor of Science, <i>honoris causa</i>
2001	UNION COLLEGE, Schenectady, New York Doctor of Laws, <i>honoris causa</i>
2002	UNIVERSITY OF LOUISVILLE, Louisville, Kentucky Doctor of Public Service, <i>honoris causa</i>
2005	STATE UNIVERSITY OF NEW YORK, Syracuse, NY Doctor of Science, <i>honoris causa</i>

- 2012 DREXEL UNIVERSITY, Philadelphia, PA
Doctor of Science, *honoris causa*
- 2013 CLAREMONT GRADUATE UNIVERSITY, Claremont, CA
Doctor of Science, *honoris causa*

HONORS

NATIONAL ACADEMY OF SCIENCES, Public Welfare Medal,
Honorary Member

INSTITUTE OF MEDICINE, Member

AMERICAN SOCIETY OF CLINICAL ONCOLOGY
Distinguished Service Award for Scientific Achievement

AMERICAN ACADEMY OF ARTS AND SCIENCES, Fellow

PHI BETA KAPPA, Amherst College

UNIVERSITY OF CHICAGO LAW REVIEW, Associate Editor

2008 PUBLIC HEALTH HERO AWARD, UC Berkeley

SIGMA XI, The Scientific Research Society of North America

BARNARD COLLEGE Barnard
Medal of Distinction

CASPAR PLATT AWARD, The University of Chicago Law School

HARVARD BLODGETT AWARD IN BIOLOGY, Amherst College

WHITING FOUNDATION GRANT-IN-AID for research at
Sloan-Kettering Institute

NATIONAL SCIENCE FOUNDATION FELLOWSHIP (declined)

JOHN WOODRUFF SIMPSON FELLOWSHIP, awarded by Amherst
College for the study of medicine

ALVAN T.--VIOLA D. FULLER AMERICAN CANCER SOCIETY
JUNIOR RESEARCH FELLOW (declined)

NATIONAL INSTITUTES OF HEALTH TRAINING FELLOWSHIP
RECIPIENT for physiology research at the Marine Biological Laboratory,

Woods Hole, Massachusetts

PHI DELTA THETA SCHOLARSHIP
DISTINGUISHED PUBLIC SERVICE AWARD
The George Washington University School of Medicine and Health Sciences

UNITED STATES DEPARTMENT OF JUSTICE, CIVIL DIVISION
Special Citation

AMERICAN SOCIETY OF PUBLIC ADMINISTRATION
National Capitol Area Chapter
President's Award for Outstanding Achievement

AMERICAN FEDERATION FOR AIDS RESEARCH (AmFAR)
Sheldon W. Andelson Public Policy Achievement Award

THE WOODROW WILSON AWARD FOR DISTINGUISHED
GOVERNMENT SERVICE Johns Hopkins University

HAL OGDEN AWARD
Association of State and Territorial Directors of Health Promotion and
Public Health Education and the U. S. Centers for Disease Control

NATIONAL ORGANIZATION FOR RARE DISEASES (NORD)
Outstanding Service to the Public Health Award

MARCH OF DIMES
Franklin Delano Roosevelt Leadership Award

CHILDREN'S HOSPITAL NATIONAL MEDICAL CENTER
Children's Research Institute Award of Academic Excellence

AMERICAN HEART ASSOCIATION
National Public Affairs Special Recognition Award for Food Labeling

ISRAEL CANCER RESEARCH FOUNDATION
President's Award

INSTITUTE FOR ADVANCED STUDIES IN IMMUNOLOGY AND AGING
Lifetime Public Service Award

AMERICAN LUNG ASSOCIATION
Special Recognition Award

UNIVERSITY OF CHICAGO ALUMNI ASSOCIATION
Professional Achievement Award (Washington, D.C. Chapter)

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Secretary's Award for Excellence in Public Service

NATIONAL KIDNEY CANCER ASSOCIATION
Progressive Leadership Award

JOHNS HOPKINS UNIVERSITY SCHOOL OF PUBLIC HEALTH
Dean's Medal

AMERICAN CANCER SOCIETY
Medal of Honor

AMERICAN HEART ASSOCIATION
Meritorious Achievement Award

WORLD HEALTH ORGANIZATION Pan
American World Health Organization World
No Tobacco Day Award

AMERICAN HEART ASSOCIATION
National Public Affairs Special Recognition Award for Tobacco

PROFESSIONAL ACHIEVEMENT CITATION, University of
Chicago Alumni Association

PENNSYLVANIA HOSPITAL Molly
and Sidney N. Zubrow Award

AMERICAN LUNG ASSOCIATION OF CONNECTICUT
Humanitarian Award

AMERICAN COLLEGE OF PREVENTIVE MEDICINE
Special Recognition Award

ASSOCIATION OF AMERICAN MEDICAL COLLEGES AND THE ROBERT
WOOD JOHNSON FOUNDATION
David E. Rogers Award for Improving Health and Healthcare of the American
People

JACOBS INSTITUTE OF WOMEN'S HEALTH
Excellence in Women's Health Award

NARAL PRO-CHOICE AMERICA
Lifetime Achievement Award

THE ASSOCIATION OF STATE AND TERRITORIAL CHRONIC DISEASE
PROGRAM DIRECTORS
Joseph W. Cullen Award for Outstanding Contributions to Chronic Disease
Prevention and Control

THE COLLEGE OF WILLIAM & MARY LAW SCHOOL
2005 Benjamin Rush Medal

CALIFORNIA CENTER FOR PUBLIC HEALTH ADVOCACY
David Kessler Award for Extraordinary Contribution to the Public
Health

BOOKS FOR A BETTER LIFE AWARD

INTERNSHIP & RESIDENCY

1981-1982 SENIOR ASSISTANT RESIDENT, Department of Pediatrics,
The Johns Hopkins Hospital

1980-1981 ASSISTANT RESIDENT, Department of Pediatrics,
The Johns Hopkins Hospital

1979-1980 INTERN, Department of Pediatrics,
The Johns Hopkins Hospital

ACADEMIC APPOINTMENTS

2003- UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
present Professor of Pediatrics
Professor of Epidemiology and Biostatistics

1997- YALE UNIVERSITY
2003 Professor of Pediatrics
Professor of Internal Medicine
Professor of Public Health

1990- ALBERT EINSTEIN COLLEGE OF MEDICINE
1997 Department of Pediatrics
(On leave) Department of Epidemiology and Social Medicine
Associate Professor of Pediatrics
Associate Professor of Epidemiology and Social Medicine

1988- ALBERT EINSTEIN COLLEGE OF MEDICINE
1990 Department of Epidemiology and Social Medicine
Assistant Professor

1986- COLUMBIA UNIVERSITY SCHOOL OF LAW
1990 Julius Silver Program in Law, Science and Technology
Lecturer on Law

David A. Kessler

Page 7

1982- ALBERT EINSTEIN COLLEGE OF MEDICINE
1990 Department of Pediatrics
Assistant Professor

SPECIAL STUDY

June JOHNS HOPKINS SCHOOL OF HYGIENE AND PUBLIC HEALTH
1987 Graduate Summer Program in Epidemiology - Pharmacoepidemiology

June YALE SCHOOL OF ORGANIZATION AND MANAGEMENT
1985 Advanced Management Studies in Health Care Management

1977-1978 HARVARD LAW SCHOOL, Special Student

RESEARCH EXPERIENCE

Summers SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
1970-1972 Division of Drug Resistance, New York, New York
Research Asst

Summer MARINE BIOLOGICAL LABORATORY, Woods Hole, Massachusetts
1972 Physiology course

1974-1975 CHILDREN'S HOSPITAL MEDICAL CENTER
Department of Surgical Research, Boston, Massachusetts
Research Associate

Summer DEPARTMENT OF HEALTH, EDUCATION and WELFARE
1976 Office of the General Counsel, Chicago, Illinois
Law Clerk

VISITING COMMITTEE

1992-1994 UNIVERSITY OF CHICAGO LAW SCHOOL

UNIVERSITY ACCREDITATION

2008-2012 WESTERN ASSOCIATION OF SCHOOLS AND COLLEGES,
Chair of LLU Accreditation Committee

2013-2015 NORTHWEST COMMISSION ON COLLEGES AND UNIVERSITIES
University of Washington

SPECIAL PROJECTS

- 1982-1988 THE ROBERT WOOD JOHNSON FOUNDATION
Program for Hospital Initiatives in Long-Term Care,
- 1989-1990 THE PEW CHARITABLE TRUSTS
THE ROBERT WOOD JOHNSON FOUNDATION
Program to Strengthen Hospital Nursing Co-Director

CORPORATE BOARD AND ADVISORY POSITIONS AND COMMITTEES

- 2011 - Present IMMUCOR
Member of Board, Chairman of Compliance Committee
- 2008 - Present TPG
Senior Advisor
- 2011 - 2014 APTALIS HOLDINGS
Member of Board, Chairman of Compliance Committee
- 2009 –2017 TOKAI
Member of Board
- 2007 GOOGLE HEALTH ADVISORY COUNCIL
- 2007 REVOLUTION HEALTH GROUP
Medical Advisory Board
- 2007 PERSEUS LLC
Advisory Board
- 2003 – 2014 FLEISHMAN HILLARD INTERNATIONAL COMMUNICATIONS
International Advisory Board
- 2000 - 2003 PERSEUS-SOROS BIOTECHNOLOGY FUND Scientific Advisory Board

ADVISORY COMMITTEES

- 2007 THE RHODES TRUST, THE RHODES SCHOLARSHIPS
Chair, California Selection Committee

2006	CENTER FOR THE ADVANCED STUDIES ON AGING, UNIVERSITY OF MIAMI External Advisory Group
2005 -2015	BROAD MEDICAL RESEARCH PROGRAM Advisory Board
2005	CLINTON SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES National Advisory Board
2003, 2013	HEINZ AWARDS (HEINZ FAMILY FOUNDATION) Awards Juror
2003	MARCH OF DIMES Chair, Prematurity Campaign in Northern California
2002 - 2004	CENTER ON ALCOHOL MARKETING AND YOUTH AT GEORGETOWN UNIVERSITY Advisory Board
2001 -	UNIVERSITY OF CHICAGO LAW REVIEW Editorial Advisory Board
2000 - 2005	JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION Oversight Committee
2000	GOVERNOR'S BLUE RIBBON COMMISSION ON MENTAL HEALTH, STATE OF CONNECTICUT Honorary Chair
2000	FILM AID INTERNATIONAL, INTERNATIONAL RESCUE COMMITTEE Advisory Board
1999	WORLD HEALTH ORGANIZATION Expert Panel on Tobacco
1997	ADVISORY COMMITTEE ON TOBACCO AND PUBLIC HEALTH (Co-Chairman with C. Everett Koop)
1993	GOVERNMENT UNIVERSITY INDUSTRY ROUNDTABLE National Academy of Sciences
1990	ADVISORY COMMITTEE ON THE FOOD AND DRUG ADMINISTRATION Chairman, Drugs and Biologics Subcommittee
1988 - 1989	NATIONAL ADVISORY COUNCIL ON HEALTH CARE TECHNOLOGY ASSESSMENT, Department of Health and Human Services, Washington, D.C. Chairman, Patient Outcomes Subcommittee

PRIOR FEDERAL COMMITTEE MEMBERSHIPS

WHITE HOUSE COMMISSION ON PRESIDENTIAL SCHOLARS

NATIONAL COUNCIL ON SCIENCE AND TECHNOLOGY

Committee on Health, Safety and Food R&D, Vice Chair

INSTITUTE OF MEDICINE

Forum On Drug Development and Regulation

INSTITUTE OF MEDICINE

AIDS Roundtable

NATIONAL TASK FORCE ON AIDS DRUG DEVELOPMENT

OFFICE OF SCIENCE AND TECHNOLOGY POLICY Federal Coordinating
Council for Science, Engineering and Technology Committee on Life Science
and Health Biotechnology Research Subcommittee, Member ex officio

BOARDS OF DIRECTORS

Current:

CENTER FOR SCIENCE IN THE PUBLIC INTEREST

DRUG STRATEGIES

Past:

AMHERST COLLEGE BOARD OF TRUSTEES

ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION

Chairman, Board of Directors

NATIONAL CENTER FOR ADDICTION AND SUBSTANCE ABUSE

COLUMBIA UNIVERSITY

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES INDEPENDENT
CITIZENS OVERSIGHT COMMITTEE OF THE CALIFORNIA INSTITUTE
FOR REGENERATIVE MEDICINE

HENRY J. KAISER FAMILY FOUNDATION

DOCTORS OF THE WORLD

YALE-NEW HAVEN HOSPITAL

CONSUMERS UNION

NATIONAL COMMITTEE FOR QUALITY ASSURANCE

NEW YORK COUNTY HEALTH SERVICE REVIEW ORGANIZATION

COMPREHENSIVE MEDICAL REVIEW ORGANIZATION

FELLOWSHIP

YALE COLLEGE Fellow,
Calhoun College

LECTURESHIPS

THE REGIS J. FALLON LECTURE SERIES ON HEALTH AND LAW
University of Chicago

GRAYSON DISTINGUISHED LECTURE
Southern Illinois University School of Law

WEINBERG SYMPOSIUM LECTURE
Harvard Medical School

THE THOMAS B. FERGUSON LECTURE
Society of Thoracic Surgeons

GEORGE E. ALTMAN, M.D. LECTURE
Beth Israel Hospital

BETH AND RICHARD SACKLER LECTURE
University of Pennsylvania

MARTIN W. WITTE LECTURE
Newport Beach Public Library and Newport Beach Public Library Foundation

HERBERT L. ABRAMS LECTURE
Harvard Medical School

GEORGE GOODMAN LECTURE
State University of New York at Stony Brook

EVNIN LECTURE
Princeton University, Woodrow Wilson School

BOYARSKY LECTURE

Law, Medicine, and Ethics, Kenan Ethics Program, Duke University

CHARTER LECTURE

The University of Georgia

GARDERE & WYNNE LECTURE

Health Law and Policy Institute, University of Houston

DISTINGUISHED LECTURE IN NATIONAL SERVICE

University of Miami

TENTH ANNUAL JOHN O. VIETA, MD LECTURE

Lenox Hill Hospital

HARPER FELLOWSHIP LECTURE

Yale Law School

DR. JAMES STEWART KAUFMAN MEMORIAL LECTURE

The Mt. Sinai Health Care Foundation

DULCY B. MILLER MEMORIAL LECTURE

Smith College

JEAN MAYER LECTURE IN NUTRITION AND FOOD POLICY

Tufts University

HENRY BARNETT DISTINGUISHED LECTURESHIP

Albert Einstein College of Medicine

MARTIN A. CHERKASKY DISTINGUISHED LECTURESHIP

Robert Wagner Graduate School of Public Service New York University

ALPHA OMEGA ALPHA DISTINGUISHED LECTURESHIP

Cornell Medical School--New York Hospital

ST. GEORGE SOCIETY LECTURESHIP

Johns Hopkins Medical School

GOVERNOR WINTHROP ROCKEFELLER DISTINGUISHED LECTURESHIP

University of Arkansas Medical School

MOLLY AND SIDNEY N. ZUBROW LECTURE

Pennsylvania Hospital

LEROY HOECK M.D. DISTINGUISHED LECTURESHIP

Children's Hospital National Medical Center

JULES AND JANE HIRSH HEALTH POLICY ADDRESS
George Washington University

JOHN S. LATTA LECTURESHIP
University of Nebraska Medical
School

PAUL K. SMITH MEMORIAL LECTURE
George Washington University

WOLK HEART FOUNDATION LECTURE
Colgate University

HASTINGS LECTURE
Association for the Advancement of Medical Instrumentation
National Heart, Lung and Blood Institute

INSTITUTE OF MEDICINE 25TH DISTINGUISHED LECTURESHIP University
of Washington

RALPH CAZORT LECTURESHIP
Meharry Medical School

DAVID M. IFSHIN MEMORIAL LECTURE
Potomac, Maryland

CHARLES C. LEIGHTON MEMORIAL LECTURE
Leonard David Institute of Health Economics
University of Pennsylvania

D. W. HARRINGTON LECTURE State
University of New York At Buffalo School of
Medicine and Biomedical Sciences

SAMUEL RUBIN LECTURE FOR THE ADVANCEMENT OF LIBERTY
Columbia University

LEO S. WEIL MEMORIAL LECTURE
Tulane Medical Center, Touro Infirmary,
and Louisiana State University School of Medicine

THOMAS PARRIN LECTURE
University of Pittsburgh School of Public Health

DAVID PACKARD LECTURE
Uniformed Services University of the Health Sciences

NORMAN E. ZINBERG LECTURE
Harvard Medical School

JOHN H. ERSKINE LECTURE
St. Jude's Children's Research Hospital

MARTIN V. BONVENTRE MEMORIAL LECTURE
The Brooklyn Hospital Center

PURVES LECTURE
Woodbridge Library, Woodbridge, Connecticut

VISITING SCHOLAR LECTURE University of
Oklahoma - Board of Regents Oklahoma Scholar
Leadership Extension Program

J. ROSWELL GALLAGHER LECTURER
Society of Adolescent Medicine

KATHERINE BOUCOT STURGIS LECTURESHIP
American College of Preventive Medicine

HELMUT SCHUMANN LECTURE
Dartmouth-Hitchcock Medical Center

50TH ANNIVERSARY COMMUNICATION LECTURE
Centers for Disease Control and Prevention

5TH JAMES BORDLEY III MEMORIAL LECTURE
Mary Imogene Bassett Hospital

TURNER LECTURE
University of California

MARIE SHULSKY MEMORIAL LECTURE ON HEALTH AND
SOCIAL RESPONSIBILITY
Fifth Avenue Synagogue, New York, New York

GERTRUDE AND G.D. CRAIN, JR. LECTURE SERIES
Medill School of Journalism, Northwestern University

GEORGE ARMSTRONG LECTURE
Ambulatory Pediatric Society

ARCO FORUM OF PUBLIC AFFAIRS
Institute of Politics, John F. Kennedy School of Government
Harvard University

PAUL LEVINGER LECTURE AND PROFESSORSHIP PRO TEM IN THE
ECONOMICS OF HEALTH CARE Brown University

ARNOLD J. SCHWARTZ MEMORIAL HEALTH LECTURE
Robert F. Wagner Graduate School of Public Service New York
University

RONALD ALTMAN MEMORIAL LECTURE
Festival of Arts, Books and Culture, Cherry Hills, New Jersey

SAMUEL MARTIN, M.D. III MEMORIAL LECTURE Division of
General Internal Medicine and Leonard Davis Institute University of
Pennsylvania

CARL J. MARTINSON, M.D. MEMORIAL LECTURESHIP ON HEALTH
PROMOTION AND DISEASE PREVENTION University of Minnesota

LEONARD SILK MEMORIAL LECTURE Mt.
Desert Island Biological Laboratories

CALDWELL LECTURE
American Roentgen Ray Society

RICHARD H. DENT LECTURE St.
George's School

ROBERT T. WONG DISTINGUISHED PROFESSORSHIP
University of Hawaii, Manoa

NIDA/American Psychiatric Association Obesity Symposium

HARVARD OBESITY COURSE

STANFORD BARIATRIC COURSE

AMERICAN BARIATRIC SOCIETY

RHODES ENDOWED LECTURE

STAFFORD LITTLE LECTURE PUBLIC LECTURES AT
PRINCETON

GERALD AND SALLY DENARDO LECTURESHIP, SANTA
CLARA UNIVERSITY

ALEX AND LENA CASPER MEMORIAL LECTURE, MIAMI
UNIVERSITY

UNIVERSITY OF VERMONT FOOD SYSTEMS
LEADERSHIP

GOOGLE LECTURE

GLOBAL STUDIES SYMPOSIUM, WHITMAN COLLEGE
Excellence in Public Service

DONALD DUNPHY LECTURE, MCCONE HOSPITAL,
UNIVERSITY OF NORTH CAROLINA

CENTER FOR GLOBAL HEALTH, STANFORD MEDICAL
SCHOOL

STANFORD UNIVERSITY: THE ETHICS OF FOOD & THE
ENVIRONMENT

STANFORD MEDICAL SCHOOL, DEPARTMENT OF
MEDICINE, GRAND ROUNDS

LEGACY WARNER SERIES LECTURE ON IMPACT OF
FAMILY AND SMOKING PREVENTION AND CONTROL
ACT

LEADING VOICES IN PUBLIC HEALTH, EAST
TENNESSEE STATE UNIVERSITY

92ND STREET YMCA PUBLIC LECTURE, NEW YORK

COMMONWEALTH CLUB OF CALIFORNIA

SAN FRANCISCO PUBLIC LIBRARY LECTURE

KANSAS CITY PUBLIC LIBRARY

YALE ROBERT WOOD JOHNSON CLINICAL SCHOLARS
PROGRAM

COMMUNITY/PUBLIC SERVICE AWARDS

NATIONAL ASSOCIATION FOR THE ADVANCEMENT OF COLORED
PEOPLE
Montgomery County Chapter
Person of the Year

LEAGUE OF WOMEN VOTERS, NEW YORK
Carrie Chapman Catt Award

COMMON CAUSE
Public Service Achievement Award

AMERICAN ACADEMY OF PEDIATRICS
Excellence in Public Service

BUSINESS WEEK
Best in Public Service

GEORGE ORWELL AWARD FOR HONESTY AND CLARITY
IN PUBLIC LANGUAGE
National Conference of Teachers of English

ANTI-DEFAMATION LEAGUE OF B'NAI BRITH
Man of Achievement Five Towns, New York

GOLDEN SLIPPER CLUB OF PHILADELPHIA
Golden Slipper Award

NATIONAL FATHER'S DAY COMMITTEE
Father of the Year Award

UNITED SENIORS HEALTH COOPERATIVE
Seniors Advocate Award

NATIONAL ASSOCIATION OF GOVERNMENT COMMUNICATORS
Communicator of the Year Award

NATIONAL CONSUMERS LEAGUE
Trumpeter Award

THE INTERNATIONAL PLATFORM ASSOCIATION
George Crile Award

AMERICAN LUNG ASSOCIATION of New York
Life and Breath Award in Public Health

CONSUMER FEDERATION OF AMERICA
Philip Hart Public Service Award

CAMPAIGN FOR TOBACCO FREE KIDS
Distinguished Service Award

MEDICAL SOCIETY OF NEW YORK, 1st District Branch
Public Service Award

ONCOLOGY NURSING SOCIETY
Public Service Award

PUBLIC VOICE FOR FOOD & HEALTH POLICY
Special Recognition Award for Advancing the Consumer Interest in Food and
Agriculture Policy

ATTENDING PEDIATRICIAN

2003 - 2013	UNIVERSITY OF CALIFORNIA, SAN FRANCISCO MEDICAL CENTER
1997-2003	YALE-NEW HAVEN HOSPITAL
1982-1990	BRONX MUNICIPAL HOSPITAL CENTER
1982-1990	NORTH CENTRAL BRONX HOSPITAL
1982-1990	MONTEFIORE MEDICAL CENTER
1982-1990	HOSPITAL OF THE ALBERT EINSTEIN COLLEGE OF MEDICINE

COMMUNITY ACTIVITIES

	SCARSDALE SCHOOL DISTRICT, Scarsdale, New York
1986-1990	Legislative Affairs Advisory Committee 1988-1990 Buildings and Facilities Advisory Committee
1990	SCARSDALE STUDENT TRANSFER EDUCATION PLAN, Board of Trustees

GENERAL INFORMATION

Address:	Office Phone:
2715 Steiner Street	(415) 929 1121
San Francisco, CA 94123	
Married:	Born:
Paulette Kessler	May 31, 1951
Two children - Elise and Ben	

MEDICAL LICENSURE

California
Connecticut (non-active)
Maryland (non-active)
New York (non-active)

PUBLICATIONS

Books

Kessler, David A., CAPTURE: UNRAVELING THE MYSTERY OF MENTAL SUFFERING, Harper, Pub. date: April 2016 Paperback : April, 2017

Kessler, David A. THE END OF OVEREATING: TAKING CONTROL OF THE INSATIABLE AMERICAN APPETITE, Rodale, 2009

Translated and Adapted:

過食にさようなら-止まらない食欲をコントロール [単行本]

KOHEI 06K0CTBJY

이 페이지 번역하기

Perché mangiamo troppo (e come fare per smetterla

Laat je niet volvreten: Hoe de voedselindustrie schade toebrengt aan onze gezondheid

Das Ende des groben Fressens Wie die Nahrungsmittelindustrie Sie zu übermäßigem Essen verleitet und was Sie dagegen tun können

Muszáj annyit enni? Hadúzenet a só, a zsír és a cukor ellen

Also: Romania, Canada, UK, Australia, India

Your Food is Fooling You: How Your Brain is Hijacked by Sugar Fat and Salt (US Young Adult Version)

Hijacked: How Your Brain is Fooled by Food (Canadian Young Adult Version)

Kessler, David A., A QUESTION OF INTENT: A GREAT AMERICAN BATTLE WITH A DEADLY INDUSTRY, Public Affairs (Hardcover 2001) (Paperback 2002)

Edited Books

Eisdorfer, Carl, Kessler, David A., Spector, Abby (eds.), CARING FOR THE ELDERLY: RESHAPING HEALTH POLICY, Johns Hopkins University Press, 1989. Includes chapter by Coombs, C., Eisdorfer, C., Feiden, K., and Kessler, D.A. "Lessons from the Program for Hospital Initiatives in Long-Term Care."

Articles

Kessler, David A., Nesbit, J.A., Westmoreland, T.M., Albright, M.B., "A Tribute to C. Everett Koop," PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 110(18):7108-9 (April 30, 2013)

Articles

McClellan M, Benner J, Schilsky R, Epstein D, Woosley R, Friend S, Sidransky D, Geoghegan C, Kessler D. An accelerated pathway for targeted cancer therapies. NATURE DRUG DISCOVERY. 2011 10(2):79-80

Kessler, David A., "Towards More Comprehensive Food Labeling," NEW ENGLAND JOURNAL OF MEDICINE, 371:193-195 (July 27, 2014)

Kessler DA, Mande JR, Scarbrough FE, Schapiro R, Feiden K. Developing the "nutrition facts" food label. HARVARD HEALTH POLICY REVIEW 2003;4:13-24

Kessler, David A., Nesbit, J.A., Westmoreland, T.M., Albright, M.B., "A Tribute to C. Everett Koop," PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, 110(18):7108-9 (April 30, 2013)

Naleid, A.M., Grimm, J.W., Kessler, David A., Sipols, A.J., Aliakbari, S., Bennett, J.L., Wells, J., Figlewicz, D.P., "Deconstructing the Vanilla Milkshake: the Dominant Effect of Sucrose on Self-administration Flavor Mixtures," APPETITE, 50(1):128-38 (January 2008)

Halme, Dina J. and Kessler, David A., "FDA Regulation of Stem Cell-Based Therapies", NEW ENGLAND JOURNAL OF MEDICINE, 355 (16): 1730-1735 (October 19, 2006)

Kessler, David A., "Alcohol Marketing and Youth: The Challenge for Public Health," JOURNAL OF PUBLIC HEALTH POLICY, 26(3):292-295 (Autumn 2005)

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APPENDIX B PRIOR TESTIMONY

Dr. David Kessler testified at trial or deposition as an expert in the following cases over more than the last seven years through March 26, 2019:

- *In re Risperdal*, Philadelphia, PA and Texas cases, including No. 2012CCV-61916-1 (Tex. Dist. Ct. filed Oct. 2, 2012 and Pledger and Walker); Wolken JCCP 4775
- *Wells v. Allergan, Inc.* No. 12-973 (W.D. Okla. filed Sept. 4, 2012); *Drake v. Allergan*, Case No. 2013 vv00234 (U.S. Dist. Ct. Burlington, Vermont)
- *In re C.R. Bard, Inc., Pelvic Repair Sys. Prods. Liab. Litig.*, MDL No. 2187 (S.D.W.V. filed July 15, 2010)
- *SB v. Ortho-McNeil-Janssen Pharm., Inc. (In re Risperdal Litig.)*, No. 100503629 (Pa. Ct. Com. Pl. filed May 27, 2010)
- *In re Yaz & Yasmin (Drospirenone) Marketing, Sales Practices & Prods. Lib. Litig.*, MDL No. 2100 (J.P.M.L. filed July 30, 2009)
- *In re Flonase Antitrust Litigation* (American Sales Company, Inc. v. Smithkline Beecham Corp.), 08-cv- 3149, United States District Court, Eastern District of Pennsylvania
- *Pharmathene, Inc. v. Siga Techs., Inc.*, No. 2627 (Del. Ch. filed Dec. 20, 2006)
- *Commonwealth v. Merck & Co.*, No. 09-1671 (Ky. Cir. Ct. filed Sept. 28, 2009) (and Utah)
- *State v. Merck & Co.*, No. 05-3700 (E.D. La. filed Aug. 5, 2005)
- *Commonwealth Care Alliance v. AstraZeneca Pharm. L.P.*, No. SUCV2005-269 (Mass. Super. Ct. filed Jan. 25, 2005)
- *Smith & Nephew, Inc. v. N.H. Ins. Co.*, No. 04-3027 (W.D. Tenn. filed Dec. 17, 2004)
- *In re Neurontin Marketing, Sales Practices & Prods. Liab. Litig.*, MDL No. 1629 (D. Mass. filed June 9, 2004)
- *Brown v. Am. Brands, Inc.*, No. 711400 (Cal Super. Ct. filed June 10, 1997)
- *In re: Actos (Pioglitazone) Prods. Lib. Litig.*, No. 11-md-2299 (W. D. La. filed Dec. 29, 2011)
- *Brown v RJ Reynolds Tobacco Company et al.*, No. 2007 CA 002855 (Fla. Cir. Ct. filed Nov. 28, 2007)
- *In re Merck & Co., Inc. Sec., Deriv. & “ERISA” Litig.*, MDL No. 1658, No. 05-2367 (D.N.J. filed May 5, 2005)
- *In re Prograf Antitrust Litigation* MDL2242, United States District Court of Massachusetts
- *In re Nexium Antitrust Litigation* MDL 2419 United States District Court, District of Massachusetts
- *Cabana v. Stryker*. Superior Court of State of California, Los Angeles
- *In Re: Fosamax Litigation*, Civil Action No. 282, (Superior Court of New Jersey, Atlantic County) and Case No. 30-2012-00547764 (Superior Court of California, Orange County)
- *Western Sugar Coop et al v. Archer-Daniels-Midland Co, et al*, U.S. District Court, Central District of California, No. 11-03473
- *H.B., et al. v. Abbott Laboratories*, No. #15-cv-702-NJR-SCW (U.S District Court, Southern District of Illinois filed June 26, 2015)
- *In re New England Compounding Pharmacy, Inc. Products Liability Litigation*, MDL No. 2419 (United States District Court of Massachusetts filed 2/14/13)
- *In re: DePuy Orthopaedics, Inc., Pinnacle Hip Implant Prods. Liab. Litig.*, MDL No. 3:11-md-02244 (N.D. Tex. filed May 24, 2011)
- *In re: Tropicana Orange Juice Mktg. & Sales Practices Litig.*, MDL No. 2353, No. 2:11-cv-07382 (D.N.J. filed Aug. 10, 2012)
- *In re Cipro Cases I and II*, Nos. 4154 & 4220 (Cal. Super. Ct., filed Feb. 25, 2002)
- *Anders v. Medtronic, Inc., et al.*, No. 1322-CC10219-02 (Mo Cir. Ct.)
- *Austin v. C.R. Bard, Inc., et al.*, Case No. 15-cv-8373 (Circuit Court of the 17th Judicial

Circuit (Div. 7), Broward County, Florida). *In re Bard IVC Filters Products Liability Litigation*, Case No. 2:15-MD- 02641-DGC.

- *In re: Zolofit Litigation*, JCCP No. 4771 (Superior Court of California, Orange County)
- *In re: Testosterone Replacement Therapy Product Liability Litigation*, MDL No. 2545 (U.S. District Court, Northern District of Illinois – Eastern Division)
- *In re: Xarelto Products Liability Litigation*, MDL No. 2592 (U.S. District Court, Eastern District of Louisiana – New Orleans Division); Philadelphia County Court of Common Pleas
- *In re: Benicar (Olmesartan) Product Liability Litigation*, Civil No. 15-2606 (U.S. District Court, District of New Jersey)
- *In re: Cook Medical, Inc. IVC Filters Marketing, Sales Practices and Product Liability Litigation*, MDL No. 2570 (U.S. District Court, Southern District of Indiana – Indianapolis Division)
- *State of Texas, ex rel. v. AstraZeneca LP, et al.*, Case No. D-1-GN-13-003530 (District Court of Travis County, Texas)
- *Council for Education and Research on Toxics v. Starbucks Corp.* et al., case number BC435759
- *In Re Asacol Antitrust* (U.S. District Court for the District of Massachusetts)
- *United States v. Merck.* ex rel., *In re: Merck Mumps Vaccine Antitrust Litigation* (U.S. Dist Ct, Eastern District of Pennsylvania)
- *Blue Cross Blue Shield v GlaxoSmithKline* (U.S. Dist Ct, Eastern District of Pennsylvania)
- *Tinsley v. Streich* (Circuit Court City of Charlottesville, Virginia))
- *People of the State of California v. Johnson & Johnson, et al.*, Case No. 37-206-00017229-CU-MC-CTL (Superior Court of the State of California, County of San Diego)
- *In re: Taxotere (Docetaxel) Products Liability Litigation*, MDL No. 2740 (U.S. District Court, Eastern District of Louisiana)

Dr. David Kessler provided sworn expert statements in the following cases over the last five years:

- *DePuy ASR Hip System Cases*, No. CJC-10-4649 (Cal. Super. Ct. filed Dec. 22, 2010)
- *Cordero v. Endoscopy Ctr. of S. Nev. LLC (In the Matter of Endoscopy Ctr. & Associated Businesses)*, No. 08-A-558091-C (Nev. Dist. Ct. filed Feb. 28, 2008)
- *Jenkins et. al. v. Medtronic, Inc. et al.*, Case No. 2:13cv02985 (W.D. Tenn.)
- *People of State of California v. Purdue Pharma L.P., et al.*, Case No: 30-2014-00725287-CU-BT-CXC (Superior Court of the State of California, County of Orange)
- *In re: Simply Orange, Orange Juice Marketing and Sales Practices Litigation*, Case #4:12-md-02361-FJG (Missouri Western District Court)
- *In re: Abilify (Aripiprazole) Products Liability Litigation*, Case No.: 3:16-MD-02734 (U.S. District Court, Northern District of Florida—Pensacola Division)

Hourly rate: 1,000/hr

APPENDIX C

National Prescription Opiate Litigation, MDL 2804 – Materials Considered

All references listed in the Report, Appendices and Schedules

BATES

ABT-MDL-KY-0000696	JAN-MS-01124875	PPLP003478494
ABT-MDL-KY-0001597	JAN-MS-01125264	PPLP003478501
ABT-MDL-KY-0001668	JAN-MS-01126863	PPLP003478683
ABT-MDL-KY-0002826	JAN-MS-01127561	PPLP003479446
ABT-MDL-KY-0004233	JAN-MS-01127792	PPLP003479945
ABT-MDL-KY-0004441	JAN-MS-01129381	PPLP003480046
ABT-MDL-KY-0004533	JAN-MS-01130624	PPLP003481935
ABT-MDL-KY-0008846	JAN-MS-01130633	PPLP003516951
ABT-MDL-KY-0011398	JAN-MS-01130740	PPLP003539723
ABT-MDL-KY-0023608	JAN-MS-01134490	PPLP003541889
ABT-MDL-KY-0023718	JAN-MS-01135994	PPLP003548234
ABT-MDL-KY-0024177	JAN-MS-01136109	PPLP003548292
ABT-MDL-KY-0025968	JAN-MS-01136453	PPLP003548330
ABT-MDL-KY-0030222	JAN-MS-01136677	PPLP003548341
ABT-MDL-KY-0031780	JAN-MS-01136730	PPLP003548342
ABT-MDL-KY-0048756	JAN-MS-01136897	PPLP003548352
ABT-MDL-KY-0050021	JAN-MS-01136974	PPLP003548357
ABT-MDL-KY-0056115	JAN-MS-01137800	PPLP003548362
ABT-MDL-KY-0058327	JAN-MS-01137972	PPLP003548367
Acquired Actavis 01190436	JAN-MS-01139135	PPLP003548372
Acquired Actavis 01389540	JAN-MS-01139478	PPLP003548378
Acquired Actavis 01444248	JAN-MS-01139518	PPLP003548416
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ENDO-CHI_LIT-00001418	MNK-T1_0000289960	PPLP004003274
ENDO-CHI_LIT-00001419	MNK-T1_0000289991	PPLP004003280
ENDO-CHI_LIT-00001419	MNK-T1_0000290041	PPLP004003282
ENDO-CHI_LIT-00001502	MNK-T1_0000290265	PPLP004003286
ENDO-CHI_LIT-00001503	MNK-T1_0000290502	PPLP004003287
ENDO-CHI_LIT-00001751	MNK-T1_0000290611	PPLP004003290
ENDO-CHI_LIT-00002063	MNK-T1_0000290934	PPLP004003293
ENDO-CHI_LIT-00002064	MNK-T1_0000291224	PPLP004003296
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ENDO-CHI_LIT-00002300	MNK-T1_0000291623	PPLP004003303
ENDO-CHI_LIT-00002411	MNK-T1_0000292978	PPLP004003306
ENDO-CHI_LIT-00002717	MNK-T1_0000293576	PPLP004003309
ENDO-CHI_LIT-00003536	MNK-T1_0000296013	PPLP004003312
ENDO-CHI_LIT-00004382	MNK-T1_0000296029	PPLP004003316
ENDO-CHI_LIT-00004499	MNK-T1_0000296035	PPLP004003319
ENDO-CHI_LIT-00005272	MNK-T1_0000296039	PPLP004003321
ENDO-CHI_LIT-00005332	MNK-T1_0000296044	PPLP004003326
ENDO-CHI_LIT-00005446	MNK-T1_0000296049	PPLP004003328
ENDO-CHI_LIT-00005607	MNK-T1_0000296056	PPLP004003333
ENDO-CHI_LIT-00005618	MNK-T1_0000296074	PPLP004003338
ENDO-CHI_LIT-00005643	MNK-T1_0000296081	PPLP004003343
ENDO-CHI_LIT-00005740	MNK-T1_0000296129	PPLP004003349
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ENDO-CHI_LIT-00005854	MNK-T1_0000296276	PPLP004003361
ENDO-CHI_LIT-00005869	MNK-T1_0000297371	PPLP004003367

ENDO-CHI_LIT-00005905	MNK-T1_0000299389	PPLP004003373
ENDO-CHI_LIT-00006051	MNK-T1_0000299390	PPLP004003379
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ENDO-CHI_LIT-00405471	MNK-T1_0000662000	PPLP004005582
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ENDO-CHI_LIT-00426024	MNK-T1_0000706894	PPLP004005702
ENDO-CHI_LIT-00426492	MNK-T1_0000708777	PPLP004005704
ENDO-CHI_LIT-00428818	MNK-T1_0000709063	PPLP004005707
ENDO-CHI_LIT-00439415	MNK-T1_0000717552	PPLP004005708
ENDO-CHI_LIT-00439576	MNK-T1_0000718230	PPLP004005710
ENDO-CHI_LIT-00452975	MNK-T1_0000724058	PPLP004005712

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ENDO-CHI_LIT-00467546	MNK-T1_0000726660	PPLP004005715
ENDO-CHI_LIT-00475399	MNK-T1_0000727866	PPLP004005716
ENDO-CHI_LIT-00477825	MNK-T1_0000730788	PPLP004005726
ENDO-CHI_LIT-00477826	MNK-T1_0000736960	PPLP004005747
ENDO-CHI_LIT-00515280	MNK-T1_0000738707	PPLP004005765
ENDO-CHI_LIT-00515283	MNK-T1_0000740034	PPLP004005777
ENDO-CHI_LIT-00515286	MNK-T1_0000740041	PPLP004005821
ENDO-CHI_LIT-00515289	MNK-T1_0000742073	PPLP004005839
ENDO-CHI_LIT-00515292	MNK-T1_0000742081	PPLP004005868
ENDO-CHI_LIT-00515295	MNK-T1_0000742106	PPLP004005884
ENDO-CHI_LIT-00515301	MNK-T1_0000742322	PPLP004005899
ENDO-CHI_LIT-00515310	MNK-T1_0000746807	PPLP004005920
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ENDO-CHI_LIT-00515316	MNK-T1_0000751417	PPLP004005952
ENDO-CHI_LIT-00515319	MNK-T1_0000751435	PPLP004005968
ENDO-CHI_LIT-00515328	MNK-T1_0000751640	PPLP004006013
ENDO-CHI_LIT-00522900	MNK-T1_0000754549	PPLP004006025
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ENDO-CHI_LIT-00536180	MNK-T1_0000754771	PPLP004006041
ENDO-CHI_LIT-00536958	MNK-T1_0000754777	PPLP004006049
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ENDO-CHI_LIT-00536960	MNK-T1_0000756159	PPLP004006061
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ENDO-CHI_LIT-00536976	MNK-T1_0000817912	PPLP004006133
ENDO-CHI_LIT-00536979	MNK-T1_0000845232	PPLP004006134
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ENDO-CHI_LIT-00536988	MNK-T1_0000857010	PPLP004006171
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ENDO-CHI_LIT-00539111	MNK-T1_0001517650	PPLP004008680
ENDO-CHI_LIT-00539112	MNK-T1_0001517743	PPLP004008695
ENDO-CHI_LIT-00539113	MNK-T1_0001518347	PPLP004008710
ENDO-CHI_LIT-00539188	MNK-T1_0001520343	PPLP004008725
ENDO-CHI_LIT-00539189	MNK-T1_0001520577	PPLP004008740
ENDO-CHI_LIT-00539190	MNK-T1_0001524367	PPLP004008755
ENDO-CHI_LIT-00539191	MNK-T1_0001524368	PPLP004008770
ENDO-CHI_LIT-00539192	MNK-T1_0001531537	PPLP004008785
ENDO-CHI_LIT-00539219	MNK-T1_0001541249	PPLP004008788
ENDO-CHI_LIT-00539225	MNK-T1_0001543091	PPLP004008801
ENDO-CHI_LIT-00539229	MNK-T1_0001545485	PPLP004008803
ENDO-CHI_LIT-00539233	MNK-T1_0001545492	PPLP004008804
ENDO-CHI_LIT-00539277	MNK-T1_0001561047	PPLP004008805
ENDO-CHI_LIT-00539320	MNK-T1_0001733508	PPLP004008806
ENDO-CHI_LIT-00539321	MNK-T1_0001749629	PPLP004008807
ENDO-CHI_LIT-00539365	MNK-T1_0001760328	PPLP004008833
ENDO-CHI_LIT-00539366	MNK-T1_0001807931	PPLP004008834
ENDO-CHI_LIT-00539367	MNK-T1_0001810304	PPLP004008835
ENDO-CHI_LIT-00539368	MNK-T1_0001853001	PPLP004008870
ENDO-CHI_LIT-00539369	MNK-T1_0001853628	PPLP004008891
ENDO-CHI_LIT-00539370	MNK-T1_0001854257	PPLP004008892
ENDO-CHI_LIT-00539371	MNK-T1_0001963782	PPLP004008894
ENDO-CHI_LIT-00539423	MNK-T1_0002034471	PPLP004008896
ENDO-CHI_LIT-00539424	MNK-T1_0002046109	PPLP004008898
ENDO-CHI_LIT-00539425	MNK-T1_0002084660	PPLP004008900
ENDO-CHI_LIT-00539426	MNK-T1_0002142446	PPLP004008902
ENDO-CHI_LIT-00539427	MNK-T1_0002157893	PPLP004008912

ENDO-CHI_LIT-00539431	MNK-T1_0002181307	PPLP004008922
ENDO-CHI_LIT-00539506	MNK-T1_0002214720	PPLP004008932
ENDO-CHI_LIT-00539510	MNK-T1_0002221235	PPLP004008942
ENDO-CHI_LIT-00539513	MNK-T1_0002289659	PPLP004008952
ENDO-CHI_LIT-00539518	MNK-T1_0002294608	PPLP004008962
ENDO-CHI_LIT-00539519	MNK-T1_0002331431	PPLP004008972
ENDO-CHI_LIT-00539520	MNK-T1_0002446841	PPLP004008982
ENDO-CHI_LIT-00539528	MNK-T1_0002475640	PPLP004008992
ENDO-CHI_LIT-00539531	MNK-T1_0002528711	PPLP004009002
ENDO-CHI_LIT-00539532	MNK-T1_0002529209	PPLP004009012
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ENDO-CHI_LIT-00539534	MNK-T1_0002530084	PPLP004009023
ENDO-CHI_LIT-00539535	MNK-T1_0002531466	PPLP004009044
ENDO-CHI_LIT-00539536	MNK-T1_0002532237	PPLP004009079
ENDO-CHI_LIT-00539537	MNK-T1_0002674394	PPLP004009100
ENDO-CHI_LIT-00539612	MNK-T1_0002715284	PPLP004009102
ENDO-CHI_LIT-00539616	MNK-T1_0002761833	PPLP004009104
ENDO-CHI_LIT-00539617	MNK-T1_0002762283	PPLP004009117
ENDO-CHI_LIT-00539620	MNK-T1_0002762751	PPLP004009129
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Amanda Stephens Hogan Deposition 1/25/2019 with Exhibits

Andrew Boyer Deposition 1/15/2019 with Exhibits

Andrew Pyfer Deposition 2/20/2019 with Exhibits

Angela Lockhart Deposition 9/10/2018 with Exhibits

Arthur F. Morelli Deposition 1/17/2019 with Exhibits

Barry Fitzsimons Deposition 6/1/2018 with Exhibits

Bonnie New Deposition 2/12/2019 with Exhibits

Brian Lortie Deposition 1/22/2019 with Exhibits

Brian Lortie Deposition 1/23/2019 with Exhibits

Brian Munroe Deposition 3/19/2019 with Exhibits

Bruce Colligen Deposition 1/22/2019 with Exhibits

Bruce Colligen Deposition 11/27/2018 with Exhibits

Bruce L. Moskowitz Deposition 8/28/2018 with Exhibits

Bruce L. Moskowitz, MD Deposition 11/13/2018 with Exhibits

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Bruce Ritchie Deposition 1/25/2019 with Exhibits

Burt E. Rosen Deposition 1/16/2019 with Exhibits

Carla Cartwright Deposition 1/17/2019 with Exhibits

Carol Marchione Deposition 1/18/2019 with Exhibits

Catherine Jackson Deposition 1/7/2019 with Exhibits

Cathy Stewart Deposition 12/11/2018 with Exhibits

Charles P. O'Brien, MD Deposition 9/20/2005 with Exhibits

Chris Sposato Deposition 1/22/2003 with Exhibits

Christine Baeder Deposition 1/24/2019 with Exhibits

Christopher M. Bauch Deposition 1/22/2019 with Exhibits

Colleen Craven Deposition 2/6/2019 with Exhibits
Colleen McGinn Deposition 12/14/2018 with Exhibits
Corinne Gillenkirk Deposition 1/16/2019 with Exhibits
Curtis Wright Deposition 8/11/2004 with Exhibits
Curtis Wright Deposition 12/19/2018 with Exhibits
Cynthia Condodina Deposition 1/9/2019 with Exhibits
David A. Myers, Jr. Deposition 12/13/2018 with Exhibits
David Everly Deposition 9/7/2018 with Exhibits
David Haddox Deposition 2/8/2019 with Exhibits
David L. Brennan Deposition 1/24/2019 with Exhibits
David Lin Deposition 12/20/2018 with Exhibits
David Myers Deposition 12/13/2018 with Exhibits
David S. Egilman, MD Deposition 12/9/2004 with Exhibits
David Tilley Deposition 10/18/2018 with Exhibits
Deanna Stacy Ayers Chick Deposition 12/13/2018 with Exhibits
Deborah Bearer Deposition 1/8/2019 with Exhibits
Demir Bingol Deposition 1/17/2019 with Exhibits
Dennis Merlo Deposition 5/26/2004 with Exhibits
Douglas Boothe Deposition 1/17/2019 with Exhibits
Drue Diesselhorst Deposition 9/5/2018 with Exhibits
Eileen Spaulding Deposition 2/5/2019 with Exhibits
Elizabeth Hightower Deposition 11/29/2018 with Exhibits
Eric Brantley Deposition 11/27/2018 with Exhibits
Erin M. Cox Deposition 1/17/2019 with Exhibits
Evan Horowitz Deposition 1/3/2019 with Exhibits
Frank Mashett Deposition 1/10/2019 with Exhibits
Gary J. Vorsanger Deposition 12/5/2018 with Exhibits

Gary J. Vorsanger Deposition 12/6/2018 with Exhibits
George Saffold Deposition 2/8/2019 with Exhibits
George Stevenson Deposition 2/15/2019 with Exhibits
Ginger Collier Deposition 1/8/2019 with Exhibits
Gregg Laws, MD Deposition 9/26/2005 with Exhibits
Hershel Jick, MD Deposition 9/19/2002 with Exhibits
Howard R. Udell Deposition 12/8/2008 with Exhibits
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Howard Shapiro Deposition 4/15/2015 with Exhibits
Jack Crowley Deposition 1/10/2019 with Exhibits
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James Lang Deposition 5/21/2004 with Exhibits
James Rausch Deposition 11/15/2018 with Exhibits
James Toothman Deposition 6/7/2004 with Exhibits
Jane Williams Deposition 12/12/2018 with Exhibits
Janet Koch Deposition 12/13/2018 with Exhibits
Jason Flanary Deposition 11/15/2018 with Exhibits
Jeannette Barrett Deposition 11/2/2018 with Exhibits
Jeffrey Kilper Deposition 2/6/2019 with Exhibits
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Jennifer Altier Deposition 8/2/2018 with Exhibits
Jimmy Adams Deposition 7/20/2004 with Exhibits
Jinping McCormick Deposition 1/9/2019 with Exhibits
Joanna Samples Deposition 9/26/2018 with Exhibits
Joe A. Brumley Deposition 9/30/2005 with Exhibits
John Adams Deposition 1/30/2019 with Exhibits
John Gillies Deposition 2/7/2019 with Exhibits

John Hassler Deposition 1/17/2019 with Exhibits
John Hassler Deposition 11/16/2018 with Exhibits
John P. Budinger Deposition 9/28/2005 with Exhibits
Joseph Tomkiewicz Deposition 11/28/2018 with Exhibits
Joyce Gaudio Deposition 1/23/2019 with Exhibits
Julie Snyder Deposition 11/2/2018 with Exhibits
Kanitha Burns Deposition 11/29/2018 with Exhibits
Karen Harper Deposition 1/25/2019 with Exhibits
Karen White Deposition 12/17/2003 with Exhibits
Karen White Deposition 5/4/2004 with Exhibits
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Kate Neely Deposition 1/8/2019 with Exhibits
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Kirk Dumont Deposition 1/18/2019 with Exhibits
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Larry Romaine Deposition 1/10/2019 with Exhibits
Laura Sippial Deposition 1/22/2019 with Exhibits
Lee Ann Storey Deposition 12/10/2018 with Exhibits
Linda Kitlinski Deposition 1/15/2019 with Exhibits
Lisa Cardetti Deposition 1/10/2019 with Exhibits
Lisa Walker Deposition 12/4/2018 with Exhibits
Lynn Phillips Deposition 2/12/2019 with Exhibits

Margaret Feltz Deposition 1/15/2019 with Exhibits

Mark Alfonso Deposition 9/15/2004 with Exhibits

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Melynda McClure Deposition 9/6/2018 with Exhibits

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Michael Perfetto Deposition 12/18/2018 with Exhibits

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Michael Wessler Deposition 1/9/2019 with Exhibits

Michele R. Dempsey Deposition 1/22/2019 with Exhibits

Nancy Baran Deposition 12/11/2018 with Exhibits

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Randy Spokane Deposition 12/5/2018 with Exhibits

Rebecca Diesselhorst Deposition 10/17/2018 with Exhibits

Richard F. Silverman Deposition 11/18/2005 with Exhibits

Richard J. Fanelli Deposition 12/6/2018 with Exhibits

Richard J. Fanelli Deposition 12/7/2018 with Exhibits

Richard Ponder Deposition 11/9/2018 with Exhibits

Richard Sackler, MD Deposition 3/7/2019 with Exhibits

Richard Sackler, MD Deposition 3/8/2019 with Exhibits

Richard Sackler, MD Deposition 8/28/2015 with Exhibits

Robert Barto Deposition 1/30/2019 with Exhibits

Robert Kaiko Deposition 11/28/2018 with Exhibits

Robert Reder, MD Deposition 1/28/2005 with Exhibits

Robert Reder, MD Deposition 1/28/2005 with Exhibits

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Ron R. Kuntz Deposition 1/23/2019 with Exhibits

Ron R. Kuntz Deposition 1/24/2019 with Exhibits

Ronald Jackson Deposition 12/18/2018 with Exhibits

Ronald Jackson Deposition 12/18/2018 with Exhibits

Ronald Wickline Deposition 11/13/2018 with Exhibits

Roxanne McGregor-Beck Deposition 1/17/2019 with Exhibits

Russell Gasdia Deposition 10/14/2003 with Exhibits
Russell Gasdia Deposition 10/5/2004 with Exhibits
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Sally Riddle Deposition 12/6/2018 with Exhibits
Sarita Thapar Deposition 1/10/2019 with Exhibits
Stacey Beckhardt Deposition 2/1/2019 with Exhibits
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Stephen Howard Deposition 9/7/2018 with Exhibits
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Steve Ochu Deposition 4/2/2008 with Exhibits
Steven Becker Deposition 12/19/2018 with Exhibits
Steven R. May Deposition 9/16/2014 with Exhibits
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Tara Chapman Deposition 12/6/2018 with Exhibits
Terrence Terifay Deposition 1/11/2019 with Exhibits
Terri Nataline Deposition 12/13/2018 with Exhibits
Thomas P. Napoli Deposition 1/17/2019 with Exhibits
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Wendell Fisher Deposition 1/26/2005 with Exhibits

William Guthrie Deposition 9/5/2018 with Exhibits

William Ratliff Deposition 12/19/2018 with Exhibits

SCHEDULE 1: GENERAL DRUG INFORMATION1

I.	PURDUE.....	2
	A. MS Contin.....	2
	B. Oxycontin.....	2
	C. Butrans	2
II.	ENDO.....	3
	A. Percocet.....	3
	B. Opana ER.....	3
	C. Opana ER (reformulated)	3
III.	JANSSEN.....	4
	A. Duragesic	4
	B. Nucynta IR.....	5
	C. Nucynta ER.....	5
IV.	TEVA	6
	A. Actiq.....	6
	B. Fentora	6
V.	ACTAVIS.....	7
	A. Kadian.....	7
VI.	MALLINCKRODT.....	8
	A. Exalgo	8
	B. Xartemis XR	9
	C. Generic Oxycontin.....	9

SCHEDULE 2: APPROVAL OF DRUG DOSAGES10

I.	PURDUE.....	11
	A. MS Contin.....	11
	B. Oxycontin.....	11
	C. Butrans	11
II.	ENDO.....	12
	A. Percocet.....	12
	B. Opana ER.....	12

	C. Opana ER (reformulated)	12
III.	JANSSEN	13
	A. Duragesic	13
	B. Nucynta IR	13
	C. Nucynta ER	13
IV.	TEVA	14
	A. Actiq	14
	B. Fentora	14
V.	ACTAVIS	15
	A. Kadian	15
VI.	MALLINCKRODT	16
	A. Exalgo	16
	B. Xartemis XR	16
	C. Generic Oxycontin	16
	SCHEDULE 3: CDC MME CONVERSION	17
	SCHEDULE 4: DEFINITIONS OF ADDICTION AND RELATED TERMS	19
	SCHEDULE 5: DEFENDANTS AND PLAINTIFFS IN THE MDL	32
	SCHEDULE 6: DIVISION OF DRUG MARKETING, ADVERTISING, AND COMMUNICATIONS LETTERS AND COMMENTS	36
I.	PURDUE	37
	A. MS Contin	37
	B. Oxycontin	72
	C. Butrans	169
II.	ENDO	187
	A. Percocet	187
	B. Opana ER	190
III.	JANSSEN	196
	A. Duragesic	196
	B. Nucynta IR	204

IV.	TEVA	206
A.	Actiq.....	206
B.	Fentora	211
V.	ACTAVIS.....	213
A.	Kadian	213

SCHEDULE 7: RELEVANT ADVISORY COMMITTEE MEETINGS AND VOTES	217
-----------------------------------------------------------------------------	------------

SCHEDULE 8: IMS SALES DATA	228
-----------------------------------------	------------

SCHEDULE 9: FDA REQUIREMENTS FOR OPIOID REMS.....	275
----------------------------------------------------------	------------

SCHEDULE 10: FDA REQUIREMENTS FOR TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF).....	287
--------------------------------------------------------------------------------------------------	------------

SCHEDULE 11: SALES REPRESENTATIVE CALL NOTES

I.	PURDUE
A.	Oxycontin
II.	JANSSEN
A.	Duragesic
B.	Nucynta IR
C.	Nucynta ER

SCHEDULE 12: LABELING CHRONOLOGIES.....	291
------------------------------------------------	------------

I.	PURDUE.....	292
A.	MS Contin.....	202
B.	Oxycontin.....	307
C.	Butrans	336
II.	ENDO	335
A.	Percocet.....	335
B.	Opana ER.....	382

	C. Opana ER (reformulated)	398
III.	JANSSEN	414
	A. Duragesic	414
	B. Nucynta IR	432
	C. Nucynta ER	437
IV.	TEVA	446
	A. Actiq	446
	B. Fentora	455
V.	ACTAVIS	468
	A. Kadian	468
VI.	MALLINCKRODT	487
	A. Exalgo	487
	B. Xartemis XR	494
	C. Generic Oxycontin	500

SCHEDULE 1

PURDUE							
Drug	NDA or ANDA	Year of Approval	Most Recent Indication	Opioid Class	Subject to RiskMap & as of When	Subject to REMS & as of When	Nature of Opioid (Immediate Release, Extended Release, Transmucosal)
MS Contin	NDA 019516	1987	MS CONTIN is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Class II	No	Yes, 2012	Extended Release
OxyContin	NDA 022272	1995	OxyContin® (oxycodone HCl) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative	Class II	Yes, 2001	Yes, 2012	Extended Release
OxyContin Reformulated	NDA 022272	2010	OxyContin® (oxycodone HCl) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative	Class II	No	Yes, 2012	Extended Release
Butrans ER	NDA 021306	2010	BUTRANS is a partial opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate	Class III	Ni	Yes, 2012	Extended Release

ENDO							
Drug	NDA or ANDA	Year of Approval	Most Recent Indication	Opioid Class	Subject to REMS& as of When	Subject to Risk MAP & as of When	Nature of Opioid (Immediate Release, Extended Release, Transmucosal)
Percocet (5/325)	ANDA 085106	1976	"the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate."	Class II	No	No	Immediate Release
Percocet (2.5/325; 5/325; 7.5/325; 10/325)	ANDA 040330	1999	"the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate."	Full opioid agonist/ NSAID	No	No	Immediate Release
Percocet (7.5/500; 10/650)	ANDA 040341	1999	"the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate."	Full opioid agonist/ NSAID	No	No	Immediate Release
Opana ER	NDA021610	2006	"the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."	Class II	No	Yes; 2006	Extended Release
Opana ER [Reformulated]	NDA 201655	2011	"the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."	Class II	Yes, 2011	No	Extended Release

JANSSEN							
Drug	NDA or ANDA	Year of Approval	Most Recent Indication	Opioid Class	Subject to RiskMap & as of When	Subject to REMS & as of When	Nature of Opioid (Immediate Release, Extended Release, Transmucosal)
Duragesic	NDA 019813	1990 ¹	<p>DURAGESIC contains fentanyl, an opioid agonist, and is indicated for the management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)</p> <p>Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)</p> <p>Limitations of use:</p> <ul style="list-style-type: none"> • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve DURAGESIC for use in patients for whom alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1) • DURAGESIC is not indicated as an as-needed (prn) analgesic 	Class II	No ²	Yes, 2012	Extended Release

¹ Janssen's supplemental new drug application (NDA 019813/S-044) providing for a matrix formulation for the transdermal delivery of fentanyl was approved on July 31, 2009. See FDA Approval Letter for NDA 019813/S-044, *available at*, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/019813Orig1s044.pdf (last visited March 26, 2019)

² Janssen first submitted a draft Risk Management Plan for Duragesic to the FDA for review and comment on July 22, 2005. JAN-MS-00213750; *see also* JAN-MS-00213780.

Nucynta IR	NDA 22-304	2008	NUCYNTA (tapentadol) tablets are indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults. □(09/2018)	Class II	No	Yes, 2018	Immediate Release
Nucynta ER	NDA 200533	2011	NUCYNTA ER is an opioid agonist indicated for the management of: • pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (1) • neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (9/2018)	Class II	No	Yes, 2012	Extended Release

TEVA							
Drug	NDA or ANDA	Year of Approval	Most Recent Indication	Opioid Class	Subject to REMS	Subject to RiskMap	Nature of Opioid (Immediate Release, Extended Release, Transmucosal)
Actiq	NDA 020747	1998	Actiq is indicated for the management of breakthrough pain in cancer patients 16 years of age and older who are already receiving and who are tolerant to around - the - clock opioid therapy for their underlying persistent cancer pain.	CII	Yes, 2011	Yes, 1998	Transmucosal Immediate Release Fentanyl (TIRF)
Fentora	NDA 021947	2006	Fentora is indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around - the - clock opioid therapy for their underlying persistent cancer pain.	CII	Yes, 2011	Yes, 2006	Transmucosal Immediate Release Fentanyl (TIRF)

ACTAVIS							
Name	NDA or ANDA	Year of Approval	Most Recent Indication	Opioid Class	Subject to REMS & as of When	Subject to RiskMAP & as of When	Nature of Opioid (Immediate Release, Extended Release, Transmucosal)
Kadian	NDA 020616	1996	“management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.”	Class II	Yes, 2009	Yes, 2007	Extended Release

MALLINCKRODT							
Drug	NDA or ANDA	Year of Approval	Most Recent Indication	Opioid Class	Subject to RiskMap & as of When	Subject to REMS & as of When	Nature of Opioid (Immediate Release, Extended Release, Transmucosal)
Exalgo ER (8mg – 12mg – 16mg dosage)	NDA 21-217	2010	<p>EXALGO is an opioid agonist indicated for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.</p> <p>Limitations of Use</p> <p><input type="checkbox"/> EXALGO is not for use:</p> <p><input type="checkbox"/> As an as-needed (prn) analgesic</p> <p><input type="checkbox"/> For pain that is mild or not expected to persist for an extended period of time</p> <p><input type="checkbox"/> For acute pain</p> <p><input type="checkbox"/> For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time</p> <p>EXALGO is only for patients in whom tolerance to an opioid of comparable potency is established.</p>	Class II	No	Yes, 2010	Extended Release
Exalgo ER (32 mg dosage)	sNDA 21-217	2012	<p>EXALGO is an opioid agonist indicated for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.</p> <p>Limitations of Use</p> <p><input type="checkbox"/> EXALGO is not for use:</p> <p><input type="checkbox"/> As an as-needed (prn) analgesic</p> <p><input type="checkbox"/> For pain that is mild or not expected to persist for an extended period of time</p> <p><input type="checkbox"/> For acute pain</p> <p><input type="checkbox"/> For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time</p> <p>EXALGO is only for patients in whom tolerance to an opioid of comparable potency is established.</p>	Class II	No	Yes, 2012	Extended Release

Xartemis XR	NDA 204031	2014	XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets is a combination of oxycodone, an opioidagonist, and acetaminophen, and is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve XARTEMIS XR for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate.	Class II	No	Yes, 2014	Extended Release
Oxycodone Hydrochloride	77-822	2008	indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative	Class II	No	Yes, 2012	Extended Release

SCHEDULE 2

PURDUE		
Drug	Dose	Date Approved
MS Contin	15 mg	09/12/1989
MS Contin	30 mg	05/29/1987
MS Contin	60 mg	04/08/1998
MS Contin	100 mg	1/16/1990
MS Contin	200 mg	11/08/91993
OxyContin	10 mg	12/12/1995
OxyContin	15 mg	9/8/2006
OxyContin	20 mg	12/12/1995
OxyContin	30 mg	9/18/2006
OxyContin	40 mg	12/12/1995
OxyContin	60 mg	12/12/1995
OxyContin	80 mg	1/16/1997
OxyContin	160 mg	3/15/2000
OxyContin Reformulated	10-160 mg	4/5/2010
Butrans	5mcg	6/20/2010
Butrans	10mcg	6/20/2010
Butrans	20mcg	6/20/2010

ENDO		
Drug	Dose	Date Approved
Percocet	5/325 mg	8/31/1976
Percocet	2.5/325 mg	7/2/1999
Percocet	5/325 mg	7/2/1999
Percocet	7.5/500 mg	7/26/1999
Percocet	10/650 mg	7/26/1999
Percocet	7.5/325 mg	11/23/2001
Percocet	10/325 mg	11/23/2001
Opana IR	5 mg	6/22/2006
Opana IR	10 mg	6/22/2006
Opana ER	5 mg	6/22/2006
Opana ER	10 mg	6/22/2006
Opana ER	20 mg	6/22/2006
Opana ER	40 mg	6/22/2006
Opana ER	7.5 mg	2/29/2008
Opana ER	15 mg	2/29/2008
Opana ER	30 mg	2/29/2008
Opana ER (Reformulated)	5 mg	12/9/2011
Opana ER (Reformulated)	7.5 mg	12/9/2011
Opana ER (Reformulated)	10 mg	12/9/2011
Opana ER (Reformulated)	15 mg	12/9/2011
Opana ER (Reformulated)	20 mg	12/9/2011
Opana ER (Reformulated)	30 mg	12/9/2011
Opana ER (Reformulated)	40 mg	12/9/2011

JANSSEN		
Drug	Dose	Date Approved
Duragesic	25 ug/hr	8/7/1990
Duragesic	50 ug/hr	8/7/1990
Duragesic	75 ug/hr	8/7/1990
Duragesic	100 ug/hr	8/7/1990
Duragesic	12.5 ug/hr	2/4/2005
Nucynta IR	100 mg	12/24/2008
Nucynta IR	75 mg	12/24/2008
Nucynta IR	50 mg	12/24/2008
Nucynta ER	250 mg	8/25/2011
Nucynta ER	200 mg	8/25/2011
Nucynta ER	150 mg	8/25/2011
Nucynta ER	100 mg	8/25/2011
Nucynta ER	50 mg	8/25/2011

TEVA		
Drug	Dose	Date Approved
Actiq	200 mcg	1998
Actiq	400 mcg	1998
Actiq	600 mcg	1998
Actiq	800 mcg	1998
Actiq	1200 mcg	1998
Actiq	1600 mcg	1998
Fentora	100 mcg	2006
Fentora	200 mcg	2006
Fentora	300 mcg	2007 ¹
Fentora	400 mcg	2006
Fentora	600 mcg	2006
Fentora	800 mcg	2006

¹ FDA website indicates the Fentora 300 microgram dose was discontinued or withdrawn for reasons other than safety and efficacy.

ACTAVIS		
Drug	Dose	Date Approved
Kadian	20MG	7/3/1996
Kadian	50MG	7/3/1996
Kadian	100MG	7/3/1996
Kadian	30MG	3/9/2001
Kadian	80MG	10/27/2006
Kadian	200MG	2/27/2007
Kadian	10MG	4/20/2007
Kadian	40MG	7/9/2012
Kadian	70MG	7/9/2012
Kadian	130MG	7/9/2012
Kadian	150MG	7/9/2012

MALLINCKRODT		
Drug	Dose	Date Approved
Exalgo ER	8 mg	03/24/2010
Exalgo ER	12 mg	03/24/2010
Exalgo ER	16 mg	03/24/2010
Exalgo ER	32 mg	07/09/2012
Xartemis XR	7.5 mg / 325 mg (acet)	03/24/2014
Oxycodone Hydrochloride	10 mg	7/24/2008
Oxycodone Hydrochloride	20 mg	7/24/2008
Oxycodone Hydrochloride	40 mg	7/24/2008
Oxycodone Hydrochloride	80 mg	7/24/2008

SCHEDULE 3

Calculating morphine milligram equivalents (MME) ¹	
OPIOID (doses in mg/day except where needed)	CONVERSION FACTOR
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥ 61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

¹ Calculating Total Daily Dose of Opioids for Safer Dosage, U.S. Department of Health and Human Services – Centers for Disease Control and Prevention, *available at* https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf (last visited March 25, 2019)

SCHEDULE 4

Addiction/Abuse				
Source	Reference	Adoption Date	Term	Definitions
World Health Organization	Lexicon of alcohol and drug terms. Geneva: World Health Organization; 1994. See page 6.	1994	Addiction, drug or alcohol	Repeated use of a psychoactive substance or substances, to the extent that the user (referred to as an addict) is periodically or chronically intoxicated, shows a compulsion to take the preferred substance (or substances), has great difficulty in voluntarily ceasing or modifying substance use, and exhibits determination to obtain psychoactive substances by almost any means.
Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition	Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 1994 See 182-183	1994	Substance Abuse	<p>The essential feature of Substance Abuse is a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances. There may be repeated failure to fulfill major role obligations, repeated use in situations</p> <p>Criteria for Substance Abuse:</p> <p>A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:</p> <p>(1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)</p> <p>(2) recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)</p> <p>(3) recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)</p> <p>(4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)</p> <p>B. The symptoms have never met the criteria for Substance Dependence for this class of substance.</p>
American Society of Addiction Medicine	American Society of Addiction Medicine Definition of Addiction. <i>available at</i> https://www.asam.org/quality-practice/definition-of-addiction (last visited March 31, 2018)	April 12, 2011	Addiction	Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

Addiction/Abuse				
Source	Reference	Adoption Date	Term	Definitions
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition	Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 2013. See page 481 - 484	2013	Substance use disorder	<p>The essential feature of a substance use disorder is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems.</p> <p>Overall, the diagnosis of a substance use disorder is based on a pathological pattern of behaviors related to use of the substance. To assist with organization. Criterion A criteria can</p> <p>be considered to fit within overall groupings of impaired control, social impairment, risky use, and pharmacological criteria. Impaired control over substance use is the first criteria grouping (Criteria 1-4). The individual may take the substance in larger amounts or over a longer period than was originally intended (Criterion 1). The individual may express a persistent desire to cut down or regulate substance use and may report multiple unsuccessful efforts to decrease or discontinue use (Criterion 2). The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects (Criterion 3). In some instances of more severe substance use disorders, virtually all of the individual's daily activities revolve around the substance. Craving (Criterion 4) is manifested by an intense desire or urge for the drug that may occur at any time but is more likely when in an environment where the drug previously was obtained or used. Craving has also been shown to involve classical conditioning and is associated with activation of specific reward structures in the brain. Craving is queried by asking if there has ever been a time when they had such strong urges to take the drug that they could not think of anything else. Current craving is often used as a treatment outcome measure because it may be a signal of impending relapse. Social impairment is the second grouping of criteria (Criteria 5-7). Recurrent substance use may result in a failure to fulfill major role obligations at work, school, or home (Criterion 5). The individual may continue substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (Criterion 6). Important social, occupational, or recreational activities may be given up or reduced because of substance use (Criterion 7). The individual may withdraw from family activities and hobbies in order to use the substance. Risky use of the substance is the third grouping of criteria (Criteria 8-9). This may take the form of recurrent substance use in situations in which it is physically hazardous (Criterion 8). The individual may continue substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (Criterion 9). The key issue in evaluating this criterion is not the existence of the problem, but rather the individual's failure to abstain from using the substance despite the difficulty it is causing.</p>
U.S. Department of Health and Human Services (HHS),	U.S. Department of Health and Human Services (HHS), Office of the Surgeon	November 2016	Addiction	The most severe form of substance use disorder, associated with compulsive or uncontrolled use of one or more substances. Addiction is a chronic brain disease that has the potential for both recurrence (relapse) and recovery

Addiction/Abuse

Source	Reference	Adoption Date	Term	Definitions
Office of the Surgeon General	General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016. See Glossary of Terms, page 1.			
Centers for Disease Control and Prevention	Opioid Basics, Commonly Used Terms, <i>available at</i> https://www.cdc.gov/drugoverdose/opioids/terms.html (last visited March 21, 2019)	August 28, 2017	Drug abuse or addiction	Dependence on a legal or illegal drug or medication.

Opioid Use Disorder				
Source	Reference	Adoption Date	Term	Definitions
Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition	Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 1994 See 249	1994	Opioid Abuse	Legal difficulties may arise as a result of behavior while intoxicated with opioids or because an individual has resorted to illegal sources of supply. Persons who abuse opioids typically use these substances much less often than do those with dependence and do not develop significant tolerance or withdrawal. When problems related to opioid use are accompanied by evidence of tolerance, withdrawal, or compulsive behavior related to the use of opioids, a diagnosis of Opioid Dependence, rather than Opioid Abuse, should be considered.
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition	Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 2013. See page 541-544.	2013	Opioid Use Disorder	<p>Opioid use disorder includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, that are used in doses greatly in excess of the amount needed for that medical condition. (For example, an individual prescribed analgesic opioids for pain relief at adequate dosing will use significantly more than prescribed and not only because of persistent pain.) Individuals with opioid use disorder tend to develop such regular patterns of compulsive drug use that daily activities are planned around obtaining and administering opioids. Opioids are usually purchased on the illegal market but may also be obtained from physicians by falsifying or exaggerating general medical problems or by receiving simultaneous prescriptions from several physicians. Health care professionals with opioid use disorder will often obtain opioids by writing prescriptions for themselves or by diverting opioids that have been prescribed for patients or from pharmacy supplies. Most individuals with opioid use disorder have significant levels of tolerance and will experience withdrawal on abrupt discontinuation of opioid substances. Individuals with opioid use disorder often develop conditioned responses to drug-related stimuli (e.g., craving on seeing any heroin powder-like substance)—a phenomenon that occurs with most drugs that cause intense psychological changes. These responses probably contribute to relapse, are difficult to extinguish, and typically persist long after detoxification is completed</p> <p>Diagnostic Criteria</p> <p>A. A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:</p> <ol style="list-style-type: none"> 1. Opioids are often taken in larger amounts or over a longer period than was intended. 2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use. 3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects. 4. Craving, or a strong desire or urge to use opioids. 5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home. 6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids. 7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.

Opioid Use Disorder				
Source	Reference	Adoption Date	Term	Definitions
				<p>8. Recurrent opioid use in situations in which it is physically hazardous.</p> <p>9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.</p> <p>10. Tolerance, as defined by either of the following:</p> <p>a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.</p> <p>b. A markedly diminished effect with continued use of the same amount of an opioid.</p> <p>Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.</p> <p>11. Withdrawal, as manifested by either of the following:</p> <p>a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal, pp. 547-548).</p> <p>b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.</p> <p>Note: This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision</p> <p>Specify if:</p> <p>In early remission: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids," may be met).</p> <p>In sustained remission: After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids," may be met).</p> <p>Specify if:</p> <p>On maintenance therapy: This additional specifier is used if the individual is taking a prescribed agonist medication such as methadone or buprenorphine and none of the criteria for opioid use disorder have been met for that class of medication (except tolerance to, or withdrawal from, the agonist). This category also applies to those Individuals being maintained on a partial agonist, an agonist/antagonist, or a full antagonist such as oral naltrexone or depot naltrexone.</p> <p>In a controlled environment: This additional specifier is used if the individual is in an environment where access to opioids is restricted.</p> <p>Coding based on current severity: Note for ICD-10-CM codes: If an opioid intoxication, opioid withdrawal, or another opioid-induced mental disorder is also present, do not use the codes below for</p>

Opioid Use Disorder				
Source	Reference	Adoption Date	Term	Definitions
				<p>opioid use disorder. Instead, the comorbid opioid use disorder is indicated in the 4th character of the opioid-induced disorder code (see the coding note for opioid intoxication, opioid withdrawal, or a specific opioid-induced mental disorder). For example, if there is comorbid opioid-induced depressive disorder and opioid use disorder, only the opioid-induced depressive disorder code is given, with the 4th character indicating whether the comorbid opioid use disorder is mild, moderate, or severe: F11.14 for mild opioid use disorder with opioid-induced depressive disorder or F11.24 for a moderate or severe opioid use disorder with opioid-induced depressive disorder.</p> <p>Specify current severity: 305.50 (F11.10) Mild: Presence of 2 -3 symptoms. 304.00 (F11.20) Moderate: Presence of 4-5 symptoms. 304.00 (F11.20) Severe: Presence of 6 or more symptoms</p>
Centers for Disease Control and Prevention	Opioid Basics, Commonly Used Terms, <i>available at</i> https://www.cdc.gov/drugoverdose/opioids/terms.html (last visited March 21, 2019)	August 28, 2017	Opioid use disorder	A problematic pattern of opioid use that causes significant impairment or distress. A diagnosis is based on specific criteria such as unsuccessful efforts to cut down or control use, or use resulting in social problems and a failure to fulfill obligations at work, school, or home, among other criteria. Opioid use disorder has also been referred to as “opioid abuse or dependence” or “opioid addiction.”

Dependence				
Source	Reference	Adoption Date	Term	Definitions
World Health Organization	Lexicon of alcohol and drug terms. Geneva: World Health Organization; 1994. See page 28.	1994	Dependence	As a general term, the state of needing or depending on something or someone for support or to function or survive. As applied to alcohol and other drugs, the term implies a need for repeated doses of the drug to feel good or to avoid feeling bad. In DSM-III-R, dependence is defined as "a cluster of cognitive, behavioral and physiologic symptoms that indicate a person has impaired control of psychoactive substance use and continues use of the substance despite adverse consequences". It is roughly equivalent to the dependence syndrome of ICD-10. In the ICD-10 context, the term dependence could refer generally to any of the elements in the syndrome. The term is often used interchangeably with addiction and alcoholism.
Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition	Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 1994 See 176-181	1994	Substance Dependence	<p>The essential feature of Substance Dependence is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems.</p> <p>Criteria for Substance Dependence</p> <p>A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:</p> <p>(1) tolerance, as defined by either of the following:</p> <p>(a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect</p> <p>(b) markedly diminished effect with continued use of the same amount of the substance</p> <p>(2) withdrawal, as manifested by either of the following:</p> <p>(a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for Withdrawal from the specific substances)</p> <p>(b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms</p> <p>(3) the substance is often taken in larger amounts or over a longer period than was intended</p> <p>(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use</p> <p>(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-</p>

Dependence				
Source	Reference	Adoption Date	Term	Definitions
				<p>smoking), or recover from its effects</p> <p>(6) important social, occupational, or recreational activities are given up or reduced because of substance use</p> <p>(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)</p>
Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition	Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 1994 See 248	1994	Opioid Dependence	Most individuals with Opioid Dependence have significant levels of tolerance and will experience withdrawal on abrupt discontinuation of opioid substances. Opioid Dependence includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if a general medical condition is present that requires opioid treatment, that are used in doses that are greatly in excess of the amount needed for pain relief. Persons with Opioid Dependence tend to develop such regular patterns of compulsive drug use that daily activities are typically planned around obtaining and administering opioids. Opioids are usually purchased on the illegal market, but may also be obtained from physicians by faking or exaggerating general medical problems or by receiving simultaneous prescriptions from several physicians. Health care professionals with Opioid Dependence will often obtain opioids by writing prescriptions for themselves or by diverting opioids that have been prescribed for patients or from pharmacy supplies.
Ohio Revised Code	Chapter 3719.011 Controlled substances definitions for use in Revised Code. Available at http://codes.ohio.gov/orc/3719.011 (last visited March 21, 2019)	July 22, 1998	Drug dependent person	(B) "Drug dependent person" means any person who, by reason of the use of any drug of abuse, is physically, psychologically, or physically and psychologically dependent upon the use of such drug, to the detriment of the person's health or welfare.
U.S. Department of Health and Human Services (HHS), Office of the Surgeon General	U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016. See Glossary of Terms, page 1.	November 2016	Dependence	A state in which an organism only functions normally in the presence of a substance, experiencing physical disturbance when the substance is removed. A person can be dependent on a substance without being addicted, but dependence sometimes leads to addiction

Tolerance				
Source	Reference	Adoption Date	Term	Definitions
World Health Organization	Lexicon of alcohol and drug terms. Geneva: World Health Organization; 1994. See page 62	1994	tolerance	A decrease in response to a drug dose that occurs with continued use. Increased doses of alcohol or other drugs are required to achieve the effects originally produced by lower doses. Both physiological and psychosocial factors may contribute to the development of tolerance, which may be physical, behavioural, or psychological. With respect to physiological factors, both metabolic and/or functional tolerance may develop. By increasing the rate of metabolism of the substance, the body may be able to eliminate the substance more readily. Functional tolerance is defined as a decrease in sensitivity of the central nervous system to the substance. Behavioural tolerance is a change in the effect of a drug as a result of learning or alteration of environmental constraints. Acute tolerance is a rapid, temporary accommodation to the effect of a substance following a single dose. Reverse tolerance, also known as sensitization, refers to a condition in which the response to a substance increases with repeated use.
Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition	Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 1994. See 176.	1994	Tolerance	Tolerance (Criterion 1) is the need for greatly increased amounts of the substance to achieve intoxication (or the desired effect) or a markedly diminished effect with continued use of the same amount of the substance.
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition	Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 2013. See page 484.	2013	Tolerance	Tolerance (Criterion 10) is signaled by requiring a markedly increased dose of the substance to achieve the desired effect or a markedly reduced effect when the usual dose is consumed.
U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016. See Glossary of Terms, page 4.	U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016. See Glossary of Terms, page 4.	November 2016	Tolerance	Alteration of the body's responsiveness to alcohol or a drug such that higher doses are required to produce the same effect achieved during initial use.

Tolerance				
Source	Reference	Adoption Date	Term	Definitions
Centers for Disease Control and Prevention	Opioid Basics, Commonly Used Terms, <i>available at</i> https://www.cdc.gov/drugoverdose/opioids/terms.html (last visited March 21, 2019)	August 28, 2017	Tolerance	Reduced response to a drug with repeated use.

Withdrawal

Source	Reference	Adoption Date	Term	Definitions
World Health Organization	Lexicon of alcohol and drug terms. Geneva: World Health Organization; 1994. See page 64.	1994	Withdrawal, conditioned	A syndrome of withdrawal-like signs and symptoms sometimes experience by abstinent alcohol- or opiate-dependent individuals who are exposed to stimuli previously associated with alcohol or drug use. According to classical conditioning theory, environmental stimuli temporarily linked to unconditioned withdrawal reactions become conditioned stimuli capable of eliciting the same withdrawal-like symptoms. In another version of conditioning theory, an innate compensatory response to the effects of a substance (acute tolerance) become conditionally linked to the stimuli associated with substance use. If the stimuli are presented without actual administration of the substance, the conditioned response is elicited as a withdrawal-like compensatory reaction.
World Health Organization	Lexicon of alcohol and drug terms. Geneva: World Health Organization; 1994. See page 64.	1994	Withdrawal, protracted	The occurrence of symptoms of a withdrawal syndrome, usually minor but nonetheless discomforting, for several weeks or months after the acute physical withdrawal syndrome has abated. This is an ill-defined condition that has been described in alcohol dependent, sedative-dependent, and opioid-dependent individuals. Psychic symptoms such as anxiety, agitation, irritability, and depression are more prominent than physical symptoms. Symptoms may be precipitated or exacerbated by the sight of alcohol or the drug of dependence, or by return to the environment previously associated with alcohol or other drug use.
Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition	Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 1994 See 184-185	1994	Substance Withdrawal	The essential feature of Substance Withdrawal is the development of a substance-specific maladaptive behavioral change, with physiological and cognitive concomitants, that is due to the cessation of, or reduction in, heavy and prolonged substance use Criteria for Substance Withdrawal A. The development of a substance-specific syndrome due to the cessation of (or reduction in) substance use that has been heavy and prolonged. B. The substance-specific syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. C. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition	Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association; 2013. See page 484.	2013	Withdrawal	Withdrawal (Criterion 11) is a syndrome that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance.

Withdrawal

Source	Reference	Adoption Date	Term	Definitions
U.S. Department of Health and Human Services (HHS), Office of the Surgeon General	U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016. See Glossary of Terms, page 1.	November 2016	Withdrawal Syndrome	A set of symptoms that are experienced when discontinuing use of a substance to which a person has become dependent or addicted, which can include negative emotions such as stress, anxiety, or depression, as well as physical effects such as nausea, vomiting, muscle aches, and cramping, among others. Withdrawal symptoms often lead a person to use the substance again.

SCHEDULE 5

LIST OF DEFENDANTS IN TRACK 1 CASES

ACTAVIS LLC

ACTAVIS PHARMA, INC. F/K/A WATSON PHARMA, INC.

ALLERGAN FINANCE LLC, F/K/A/ ACTAVIS, INC., F/K/A WATSON
PHARMACEUTICALS, INC.

ALLERGAN PLC F/K/A ACTAVIS PLC

AMERISOURCEBERGEN DRUG CORPORATION

ANDA, INC.

CARDINAL HEALTH, INC.

CEPHALON, INC.

CVS INDIANA, LLC

CVS RX SERVICES, INC.

DISCOUNT DRUG MART, INC.

ENDO HEALTH SOLUTIONS INC.

ENDO PHARMACEUTICALS, INC.

H.D. SMITH HOLDING COMPANY

H.D. SMITH HOLDING COMPANY (Cuyahoga only)

H.D. SMITH HOLDINGS LLC

H.D. SMITH HOLDINGS, LLC (Cuyahoga only)

H.D. SMITH LLC D/B/A HD SMITH F/K/A H.D. SMITH WHOLESALE DRUG CO.

H.D. SMITH, LLC D/B/A H.D. SMITH, F/K/A H.D. SMITH WHOLESALE DRUG CO.
(Cuyahoga only)

HBC SERVICE COMPANY

HEALTH MART SYSTEMS, INC.

HEALTH MART SYSTEMS, INC. (Cuyahoga only)

HENRY SCHEIN MEDICAL SYSTEMS, INC.

HENRY SCHEIN MEDICAL SYSTEMS, INC. (Summit only)

HENRY SCHEIN, INC.

HENRY SCHEIN, INC. (Summit only)

INSYS THERAPEUTICS, INC.

JANSSEN PHARMACEUTICA, INC. N/K/A JANSSEN PHARMACEUTICALS, INC.

JANSSEN PHARMACEUTICALS, INC.

JOHNSON & JOHNSON

MALLINCKRODT LLC

MALLINCKRODT PLC

MCKESSON CORPORATION

MIAMI-LUKEN, INC.

NORAMCO, INC.

ORTHO-MCNEIL- JANSSEN PHARMACEUTICALS, INC. N/K/A JANSSEN
PHARMACEUTICALS, INC.

PAR PHARMACEUTICAL COMPANIES, INC. F/K/A PAR PHARMACEUTICAL
HOLDINGS, INC.

PAR PHARMACEUTICAL, INC.

PRESCRIPTION SUPPLY, INC.

PURDUE PHARMA, INC.

PURDUE PHARMA, L.P.

RITE AID OF MARYLAND, INC. D/B/A RITE-AID MID-ATLANTIC CUSTOMER
SUPPORT CENTER, INC.

SPECGX LLC

TEVA PHARMACEUTICAL INDUSTRIES, LTD.

TEVA PHARMACEUTICALS USA, INC.

THE PURDUE FREDERICK COMPANY, INC.

WALGREEN CO.

WALGREEN EASTERN CO.

WALMART INC. F/K/A WAL-MART STORES, INC.

WATSON LABORATORIES, INC

LIST OF PLAINTIFFS IN TRACK 1 CASES

THE COUNTY OF SUMMIT, OHIO

THE COUNTY OF CUYAHOGA, OHIO

SCHEDULE 6

Warning Letters

PURDUE			
Product	Date	Contents	BATES
MS Contin	10/15/1993	<p>FDA sent Purdue a Notice-of-Violation Letter for the following promotional materials:</p> <ol style="list-style-type: none">1. Reprint of the Bloomfield study, published in <i>Clinical Pharmacology and Therapeutics</i>2. Bloomfield reprint carrier3. DDMAC's letter of March 26, 1993 re: Oramorph SR <p>Reprint of Bloomfield Study Claim: "M.S. Contin tablets were nearly twice as potent as Oramorph S.R. tablets" FDA Response: FDA considered the claim misleading for several reasons:</p> <ol style="list-style-type: none">1. The claimed 2-fold difference comes from Table I in "Analgesic potency estimates of M.S. Contin tablets relative to Oramorph S.R. tablets." "The 95% confidence intervals for the potency estimates range from 0.75-11. This range indicates there is <u>no</u> difference between the two drugs in this trial."2. "The differential superiority claim made for M.S. Contin 90 mg compared with Oramorph S.R. 90 mg is the result of an arbitrary extrapolation technique of the data...It is unlikely that differences between M.S. Contin and Oramorph S.R. exist."3. "Comparisons of two drugs' effectiveness must be derived from 'substantial clinical experience.' The Agency has defined substantial clinical experience as at least two adequate and well-controlled studies. If the Bloomfield study showed a statistical difference in analgesic potency, results from only one study would not meet the requirements for substantial clinical experience." <p>Bloomfield Reprint Carrier</p> <ol style="list-style-type: none">1. "Any references to the Bloomfield article that is reproduced in the reprint carrier is misleading and therefore, unacceptable for distribution."2. "Any reference to open-label study represented in the table on page 4 of the reprint carrier is unacceptable..."3. Following statements are misleading:<ul style="list-style-type: none">• "No other drug is therapeutically equivalent to M.S. Contin."• "The FDA's <u>Approved Drug Products with Therapeutic Equivalence Evaluation</u> ("The Orange Book") rates Oramorph S.R. as a "BC" product-meaning that it is <u>not</u> considered to be therapeutically equivalent for generic substitution with M.S. Contin Tablets."	PDD8006000028

		<p>DDMAC Letter</p> <p>“The distribution of the DDMAC letter of March 26, 1993, by Purdue Frederick implies a comparison between M.S. Contin and Oramorph S.R.... Comparisons between two drug products must be demonstrated by substantial clinical experience. The DDMAC letter does not constitute substantial clinical experience, and is therefore, unacceptable for distribution by Purdue Frederick.”</p> <p>Action Steps: Purdue required to do the following:</p> <ol style="list-style-type: none"> 1. Immediately discontinue dissemination of the Bloomfield Study and related materials and the March 26, 1993 DDMAC letter 2. Provide in writing documentation of compliance 3. Submit a list of all promotional materials that will be discontinued <p>Submit a list of all promotional materials that will remain in use</p>	
MS Contin	11/20/1996	<p>Regarding “reprints” of Michael H. Levy article, <i>“Pharmacologic Management of Cancer Pain.”</i></p> <p>Violations</p> <p>“Promotional materials contain false and/or misleading statements and suggestions that MS Contin is superior to other analgesics, either in effectiveness, safety, or other parameters, in the management of cancer pain.”</p> <ul style="list-style-type: none"> • “Specifically, the article suggests that controlled-release MS Contin is superior to other opioid analgesics for chronic cancer pain.” <p>Repetitive Conduct</p> <p>“The dissemination of these materials represents a repetitive course of violative conduct by Purdue in the promotion of MS Contin. Purdue has repeatedly disseminated materials that contain unsupported claims that MS Contin is superior to other analgesics...DDMAC determined that these were false and/or misleading on several occasions and communicated this to Purdue in letters dated October 15, 1993, March 25, 1994, June 7, 1994, July 7, 1994 and October 3, 1994, and at a meeting between FDA and Purdue on March 24, 1994.”</p> <p>Conclusion and Requested Action</p> <p>Purdue should propose a corrective action, including mailing a “Dear Healthcare Professional” letter. The corrective action plan should include: immediately ceasing all dissemination of the materials, a complete listing of all advertising and promotional materials that will remain in use and those that will be discontinued, within 15 days disseminate a message to all sales representatives instructing them to immediately cease all dissemination.</p>	PDD8006000529

Company Responses to Warning Letters

PURDUE			
Product	Date	Contents	BATES
MS Contin	12/8/1993	<p>Purdue's response to the FDA's Notice-of-Violation letter from 10/15/1993.</p> <p>Bloomfield Study</p> <ul style="list-style-type: none"> • This paper was accepted in a peer review journal and utilized data developed in an adequate, well-controlled study • The results are supported by the recently completed study of Stephen A. Cooper, D.M.D., Ph.D. • Purdue submitted the statements of 4 experts supporting the methods and findings of the Bloomfield and Cooper studies. "These experts agree that the Bloomfield study and the Cooper study demonstrate that MS Contin is significantly more effective than Oramorph SR at equal milligram doses." • "Together, the Bloomfield and Cooper studies provide substantial experience to show the greater efficacy of MS Contin over Oramorph SR on a milligram basis. The findings of the Bloomfield and Cooper studies are further substantiated by at least two previous reports showing that that the pharmacokinetic parameters for these two drugs differ." • "The circumstances and issues to which the Bloomfield article and reprint carrier are directed must be understood. These documents were distributed to correct many grossly false and misleading comparative promotions that Roxane Laboratories has distributed against MS Contin for more than five years... We have made numerous submissions to your office regarding these false and misleading comparative claims." • "The Bloomfield reprint and carrier were distributed to refute the false claims made against MS Contin by Roxane Laboratories. Our claim, which is fully documented by these scientific studies, is that MS Contin and Oramorph SR are different and cannot be assumed to be therapeutically equivalent." <p>Bloomfield Reprint Carrier</p> <ul style="list-style-type: none"> • Purdue believes the use of the open-label studies was appropriate and justified. "Our objective was to rebut and correct the flagrantly false comparisons made by Roxane Laboratories, in which Roxane used some early MS Contin studies designed to evaluate both b.i.d. and t.i.d. dosing, to imply that the subjects who were never titrated on a b.i.d. schedule were failures on that regimen." • "Further, the six studies...are fully confirmed by the well-controlled clinical studies that supported the 	PDD8006000067

		<p>approved 12-hour dosage schedule for MS Contin.”</p> <ul style="list-style-type: none"> “Frankly, we came to believe the FDA could not curb the activity of Roxane Laboratories, and that our self-imposed restraint against counter-promotion was increasingly harmful to MS Contin.” <p>Summary</p> <ul style="list-style-type: none"> “FDA must not censor the dissemination of accurately presented and truthful scientific data, particularly when it is relevant to refut the false claims distributed for years by Roxane Laboratories. Roxane is not entitled to be protected against the use of valid clinical studies which prove its comparative claims are false.” “The Bloomfield study and the Cooper study are adequate, well-controlled studies confirming that there is a significant difference in relative potency on a milligram basis and consequently clinical effectiveness in favor of MS Contin.” 	
MS Contin	11/26/1996	<p>Purdue’s initial response to the FDA warning letter dated 11/20/1996. Purdue advised the FDA that they sent a memorandum to the sales force to stop distribution of the two subject documents.</p> <p>PPLP also advised that they “do not agree that the three statements cited in your letter are false or misleading, as they are presented within the context and content of Dr. Levy’s comprehensive review of pain management in the journal article, and in the reprint and booklet forms disseminated by Purdue.”</p>	PDD8006000533
MS Contin	12/12/1996	<p>Purdue’s response to the FDA warning letter dated 11/20/1996. The DDMAC letter concluded that the following statements made in the Levy reprint were false and misleading, because they state or suggest that the controlled-release morphine (MS Contin) is superior to other opioid analgesics for chronic cancer pain:</p> <ul style="list-style-type: none"> “Controlled-release morphine (MS Contin) is the best opioid analgesic for pain prevention in patients with chronic cancer pain.” “MS Contin is recommended over Oramorph based on the smaller size and the color-coding of its tablets and the availability of its 15-mg and 200-mg dosage forms.” “Because of its 12-hour dosing interval, MS Contin is the preferred opioid analgesic for these patients along with PRN supplements of MSIR for breakthrough pain.” <p>PPLP has reviewed these statements as they are presented within the entire Levy article. “Each statement must be read in the context of the entire article because the reprints in which they appear do not highlight or emphasize them in any way.”</p> <ul style="list-style-type: none"> “Dr. Levy’s comments reflect his opinions as an expert specialist, regarding the role of controlled-release morphine in patients with chronic cancer pain. His statements in the context in which they are made do not 	PDD8006000551

		<p>suggest that controlled release morphine is superior in effectiveness or safety to other opioid analgesics.”</p> <ul style="list-style-type: none"> • “Dr. Levy states on the first page...that his ‘Recommendations concerning specific generic or branded products are based on the author’s analysis of the literature and clinical experience and are not meant to exclude other pharmacologic agents with the same drug class or other branded products of the same generic drug.” • “...it is absolutely clear that Dr. Levy does not suggest that controlled-release morphine, or MS Contin, are superior in analgesic effect to other strong opioids.” • “In context, the first statement referring to ‘Controlled-release morphine (MS Contin) [as] the best opioid analgesic,’ clearly means it is recommended because of the convenience of oral dosing at extended intervals.” • “Your letter comments that the Levy reprint was modified in a manner not relevant to your objections. It should be noted that the parts of the article we deleted referred to unapproved, off-label indications for the use of some products, in order to assure regulatory compliance.” <p>Repetitive Conduct</p> <ul style="list-style-type: none"> • “We strongly disagree that the dissemination of the Levy reprint ‘represents a repetitive course of violative conduct.’ First, the dissemination of the Levy reprint was not violative. Secondly, we firmly disputed each of the allegations in the prior letters communicated to us by DDMAC. No finding has been made in any forum that the prior claims, unrelated as they are to the issues in the Levy reprint, were false or misleading. We believed that a mutual agreement had been reached satisfactory to fully resolve the prior concerns of DDMAC. In each instance we accommodated your office to avoid conflict, but we absolutely disagreed that the prior disputed statements in MS Contin promotion were not true or not supported by adequate scientific evidence.” <p>Corrective Actions Requested</p> <ul style="list-style-type: none"> • Purdue “concludes that the Levy reprint and booklet form we disseminated do not represent or suggest that controlled-release morphine and MS Contin are superior in safety or efficacy to other strong opioids. Therefore, no corrective action is appropriate.” • “Your letter was disseminated to our sales representatives and marketing personnel, with our initial instruction directing that the Levy reprint booklet not be used. This reply letter will also be disseminated to them, with our direction to discontinue and destroy the Levy reprints for the reason stated above.” 	
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Promotional Material Review & DDMAC Discussions

PURDUE				
Product	Date	To/From FDA	Contents	BATES
MS Contin	1/24/1992	From FDA	Letter from the FDA to Purdue regarding an industry complaint about the promotional theme for MS Contin. The complaint was against the tagline, "An End To The Reign of Pain" because it suggests that MS Contin will permanently end pain, which is false and misleading.	PDD8006000024
MS Contin	2/7/1992	To FDA	<p>Purdue's response to the FDA letter from 1/24/1992. The tagline has been used for MS Contin since 1990 and until this letter Purdue had received no complaint about the tagline.</p> <p>"The interpretation given in the industry objection, that the tagline promises a permanent end to pain for patients treated with MS Contin, is in our opinion extremely unrealistic and unreasonable within the context of each piece of labeling using the tagline, and given the common knowledge of the targeted professional audience."</p> <p>"The intended meaning of the tagline refers to the goal of providing effective analgesia to end the 'reign' of chronic, moderate to severe pain, as it affects the daily lives and activities of patients suffering such pain."</p> <p>Purdue agreed to stop using the tagline to avoid conflict with the FDA.</p>	PDD8006000025
MS Contin	2/25/1992	From FDA	FDA's response to Purdue's letter on 2/7/1992. The FDA reviewed the submissions from Purdue and had no objection to their distribution. "We will expect however, according to your letter, that no further distribution of this labeling will made [sic] after that date and the current tagline will be revised."	PDD8023017621
MS Contin	10/20/1993	Call with FDA	Call with the FDA to discuss the Partners Against Pain brochure "Cancer pain, prevalent but controllable." FDA pointed out that "nowhere in the brochure do we mention contraindications, warnings, drug interactions and that it was a controlled substance...the Package insert wasn't enough and doesn't replace our need to mention these issues in the ad."	PDD8023020007
MS Contin	11/18/1993	To FDA	Initial submission of promotional materials for MS Contin 200 mg including 12 announcement letters to the medical profession and trade, press release,	PDD8023020367

			retail sell sheet, visual aid, approved package insert.	
MS Contin	12/3/1993	From FDA	<p>Letter from the FDA advising Purdue that their Hospital Panel submitted to the FDA for review is in violation of the FDCA.</p> <p>Objections</p> <ul style="list-style-type: none"> FDA objects to the sentence, “Reduces the anxiety associated with the anticipation of breakthrough pain with PRN regimens.” Claim is false and misleading because MS Contin isn’t indicated as anxiolytic. The panel lacks fair balance. “MS Contin’s approved labeling carries many warnings, risks, and precautions, yet the panel only states that MS Contin ‘may be habit forming.’” <p>DDMAC requested that they discontinue using the panel immediately as well as any promotional materials, which make the same or similar claims.</p>	PDD8006000118
MS Contin	12/9/1993	To FDA	Purdue’s response to an FDA telephone request for copies of references cited in an MS Contin 200 mg visual aid.	PDD8023020445
MS Contin	12/17/1993	To FDA	<p>Purdue’s response to the FDA’s letter from 12/2/1993 regarding the Hospital Panel.</p> <ul style="list-style-type: none"> Objection: “Reduces the anxiety associated with the anticipation of breakthrough pain with PRN regimens” is false and misleading because MS Contin isn’t indicated as anxiolytic. Purdue response: “Our statement about the reduction of anxiety does not imply that MS CONTIN is an anxiolytic drug. Rather, the statement describes a well-established analgesic principle which is overwhelmingly supported by current medical consensus. This principle recognizes the need for around-the-clock, rather than PRN analgesic regimens to prevent or manage pain and reduce the fear, apprehension, and anxiety related to anticipation of pain.” Objection: Panel lacks fair balance because there are no references to many warnings, risks, and precautions. Purdue Response: The Panel meets the required standards of disclosure under Section 201(n). “We do not agree that the concept of ‘fair balance’ in promotional <u>labeling</u> 	PDD8006000120

			requires a prominent statement of either 1) <u>all</u> side effects, warnings, precautions, and contraindications that are already included in the accompanying full disclosure; 2) a <u>brief summary</u> of such information, or 3) some selected information that is deemed to be most important.”	
MS Contin	12/22/1993	To FDA	Purdue advises that the visual aid submitted on 11/18/1993 was a preliminary draft which has since been superseded. Purdue submits the correct version.	PDD8023020716
MS Contin	12/23/1993	From FDA	<p>FDA letter to Purdue on the review of the proposed launch materials for MS Contin 200 mg. The FDA’s opinion is that the proposed materials are not acceptable.</p> <p>Overall Objections</p> <p>MS Contin 200 was approved was use in a special population of patients with a high opioid demand that have shown to be opioid tolerant. “The entire launch and advertising campaign, however, fails to mention the significant risks associated with the product. Therefore, all promotional materials must be revised to include prominent states...similar to:</p> <ul style="list-style-type: none"> • The 200mg dosage of MS Contin is appropriate for use only in the small number of opioid tolerant patients who have already been titrated to a stable analgesic regimen using lower strengths of MS Contin or other opioids. • MS Contin 200 should not be used as the initial opioid analgesic in the management of pain. • MS Contin 200 has a significant number of risks, warnings, and precautions, other than it ‘may be habit forming.’ These must be clearly described and prominently displayed.” <p>Sell Sheets</p> <p>“...we are troubled by the sell sheet’s offering of a \$70 rebate directly to pharmacists for each bottle sold. This product belongs in a minority of pharmacies, dealing with a small number of patients, and is neither useful nor safe if treated as just another strength of MS Contin.”</p> <p>Visual Aid</p> <p>Is unacceptable because:</p> <ul style="list-style-type: none"> • “There is excessive prominence given to the ‘200mg’ in the escalation of doses. The 	PDD8006000136

			<p>impression relayed is that the 200mg strength may be used as an initial dose in place of lower doses of Ms Contin.</p> <ul style="list-style-type: none"> • There is no information related to adverse effects, risks, or precautions related to this very high 200mg dose. • The statement ‘For use in opioid tolerant patients’ must be significantly more prominent, for the reasons cited previously.” 	
MS Contin	1/5/1994	From FDA	<p>FDA’s response to Purdue’s letter from 12/17/1993 on the use of claim “reduces the anxiety associated with the anticipation of breakthrough pain with PRN regimens.” DDMAC is willing to let Purdue use the claim but they must “also inform the reader that MS Contin, like all analgesic agents administered on a fixed-dose schedule, has the potential to reduce anticipatory anxiety related to breakthrough pain once chronic pain is relieved.”</p>	PDD8006000129
MS Contin	1/10/1994	To FDA	<p>Purdue’s response to the FDA letter from 12/23/1994.</p> <p>Purdue agrees that it is important to make it clear to physicians that MS Contin 200 mg has a limited patient population. However, they disagreed with the FDA’s categorization of their drug approval and limitations of its distribution. MS Contin was not approved as an Orphan Drug as stated by the FDA in their letter. Furthermore, Purdue argued that the FDA did not dictate tablet size, shape, packaging, etc.</p> <p>“The packaging and labeling information clearly and conspicuously restricts use to only opioid tolerant patients. Therefore, Purdue Frederick believes that this approved 200 mg is adequately positioned so that there is minimal risk of it being prescribed in error.” Purdue agreed to make more prominent that 200 mg is intended only for use in opioid tolerant patients.</p> <p>Purdue disagreed with the FDA on the \$70 rebate to pharmacists. “This is not a drug that is sampled to physicians, and, because of the limited patient population for which it is appropriate, greater inducements than usual are necessary to encourage the stocking of this low volume product at the wholesale and retail levels.”</p>	PDD8006000136
MS Contin	1/12/1994	From FDA	<p>The FDA’s response to Purdue’s 1/10/1994 letter. The FDA acknowledges Purdue’s intention to prominently display “for use in opioid tolerant</p>	PDD8006000164

			patients only.” However, the announcement letters, press release, and Visual Aid “fail to adequately convey important risk, warning, and precaution information vital to the safe use of MS Contin 200 mg. Because of this, the pieces would be considered to be misleading...” There was no mention of corrective measures in Purdue’s letter. The FDA requests copies of revised promotional materials.	
MS Contin	1/24/1994	From FDA	<p>The FDA’s letter in response to Purdue’s letter from 12/8/1993 responding to the 10/15/1993 Notice of Violation letter.</p> <p>The Bloomfield Study DDMAC re-reviewed the study and continued to find the study objectionable. In addition, to the reasons cited in the 10/15/1993 letter, the FDA objected to the following items:</p> <ul style="list-style-type: none"> • “The use of a single-dose, single pain model study in patients experiencing acute post-surgical pain to support promotional or superiority claims for a drug which is a strong opioid analgesic intended for use for ‘more than a few hours.’” • Statement “the 90mg MS Contin dose was statistically significantly better than the 90mg Oramorph SR dose group at hours 7 and 8 (data not shown).” “The data omission, in conjunction with the data presented in Table III, raises the question whether there is a statistically significant difference in long-term pain relief between these two groups.” • Data in Table II presents statistical comparisons between MS Contin 90 mg, 30 mg, and Oramorph SR 30 mg but there is no presentation of statistical comparisons between MS Contin 90 mg and Oramorph SR 30 mg. • “None of the secondary efficacy variables...show superiority of the MS Contin 90 mg over Oramorph SR 90 mg...” • The statement “MS Contin tablets provided greater peak, total, and duration of analgesia, particularly in total effect as measured by TOTPAR and SPID” is misleading. No comparisons were made between MS Contin 90 mg and Oramorph 90 mg. No evidence supports this statement. • The study involves only woman and therefore restricts the patient population. 	PDD8006000075

The Cooper Study

DDMAC objected to the use of this article for the following reasons:

- “...there is no presentation of data related to previous analgesic regimens, specific types of orthopedic procedures, length of time between the procedure and study entry, or need for long-term opioid analgesia. Therefore, because this study involved a single pain model, it cannot support by itself the generalization to all pain models.”
- The statement “MSC 60mg demonstrated greater **numerical** (our emphasis) efficacy than OSR 60mg for many of the summary analgesic variables” is misleading. The confidence intervals for both overlap significantly. “Without presentation of appropriate statistical tests, there is no evidence from this statement that numerical efficacy equates to statistical significance...”
- A higher percentage...of patients in the MS Contin 60 mg group received a rescue dose and there isn’t an indication of how the PID score for the patients was affected.
- “The study concludes that MSC 60mg provided the greatest peak analgesic effect and was more efficacious than OSR 60mg through the sixth hour with statistical significance at one, two, and three hours post-dosing. This conclusion is misleading because, at greater than 6 hours, there is no evidence that either agent provided any differential pain relief.”

Reviewers Statements

DDMAC objected to these testimonials. “Such statements do not provide any additional information. Moreover, persons who collaborate closely with the sponsor, such as Purdue Frederick cannot provide objective analyses of studies making superiority claims.”

Promotional Activities

The FDA responds to Purdue’s arguments from their 12/8/1993 response.

Purdue’s argument on pharmacokinetic studies:

- “Such studies, however, do not support comparative claims and do not necessarily

			<p>relate to clinical use in any particular patient population.”</p> <ul style="list-style-type: none"> • The agency considers comparative claims to be efficacy claims and such claims must be supported by “at least two adequate and well-controlled studies.” <p>Purdue’s argument on the use open-label studies as appropriate and justified</p> <ul style="list-style-type: none"> • The FDA disagrees and believes neither is true. • “Open-label studies cannot support efficacy or enhanced safety. At best, large open-label studies can only demonstrate the existence of certain adverse events that did not appear in clinical trials.” <p>Purdue’s argument on bioequivalency</p> <ul style="list-style-type: none"> • “Although these products have not been demonstrated to be therapeutically equivalent, neither has been demonstrated to be superior to the other.” • “...it is misleading to suggest that these products are equivalent, and it would be equally misleading to suggest that a lack of equivalence meant that there was some element of superiority between products.” <p>Purdue’s speculation about competitive activity</p> <ul style="list-style-type: none"> • FDA disagreed with Purdue’s justification for disseminating NOV letter to Roxane. • Purdue agreed not to distribute the Bloomfield article or reprint carrier for 60 days. 	
MS Contin	1/26/1994	To FDA	<p>Response to the FDA’s letter from 1/5/1994 advising them they could continue using the phrase “reduces the anxiety associated with the anticipation of breakthrough pain with PRN regimens.” Purdue advises they will release this Panel for use.</p>	PDD8006000130

MS Contin	2/8/1994	To FDA	<p>Purdue's response to the FDA letter from 1/24/1994 discussing the Bloomfield and Cooper studies. Purdue disagrees with the FDA's objections.</p> <ul style="list-style-type: none"> • "We contend that the single-dose pain model designs employed in the studies are established, scientifically valid measures of comparative analgesic efficacy. In addition, we believe that each study's conclusions are supported by the data." • Purdue is upset by the characterization of the expert opinions as "testimonials." <p>Purdue believes the issues required discussion with the FDA scientists and/or statisticians.</p>	PDD8006000081
MS Contin	3/2/1994	To FDA	Purdue letter to the FDA following up on a request for a meeting to discuss the Bloomfield and Cooper studies and to confirm a meeting that same day.	PDD8023021308
MS Contin	3/10/1994	To FDA	Submission of Cancer Pain booklet for review	PDD8006000240
MS Contin	3/16/1994	To FDA	Submission of revised Visual Aid for the promotional launch materials for MS Contin 200 mg	PDD8006000197
MS Contin	3/24/1994	Meeting with FDA	Meeting to discuss efficacy of MS Contin and Oramorph SR	PDD8023021409
MS Contin	3/25/1994	From FDA	<p>FDA's letter to Purdue advising that they have reviewed the Cancer Pain brochure submitted on 3/10/1994 and found it false and misleading for the below reasons:</p> <ul style="list-style-type: none"> • Study by Savarese wasn't conducted in a "major U.S. cancer center" and the study was conducted on patients who "were domiciled in the clinic" but there is no indication of what type of clinic was utilized. • The Meed study was an open-label preference study and the authors stated, "a built-in bias was that all the patients in this study were people who...were dissatisfied with their existing analgesic regimen." The data is misleading because Purdue doesn't disclose this bias. • "The efficacy bar chart is misleading because there is no documentation of how the 93% was derived. Because no individual data is presented, it is unknown whether all the patients were comparable and whether preference was measured consistently across each study." • "The safety section is misleading because the reporting of adverse effects is 	PDD8006000240

			<p>inadequate.”</p> <ul style="list-style-type: none"> Headline “for equal analgesia, compare the dosing schedules” is misleading ‘because it implies that the doses of these products are equipotent.” 	
MS Contin	4/12/1994	To FDA	Purdue’s response to the FDA’s letter from 3/25/14 regarding the Cancer Pain booklet. Purdue advises that they have discontinued distribution of the booklet and will not disseminate until they respond to the FDA’s objections.	PDD8006000246
MS Contin	5/9/1994	To FDA	Submission of proposed combined advertisement for MS Contin 200 mg and the Partners Against Pain campaign.	PDD8006000223
MS Contin	5/10/1994	To FDA	<p>Purdue’s full response to the FDA’s letter from 3/25/14 regarding the Cancer Pain booklet. The reference citations in the booklet were wrong or incomplete in several places and thus the booklet was discontinued. Purdue prepared a revised version and requested comment from the FDA on 5 of the proposed changes.</p> <ul style="list-style-type: none"> The Savarese citation was incorrect and would be fixed. Objection regarding the statement, “‘a built-in bias was that all people in this study were people who...were dissatisfied with their existing analgesic regimen.’ This observation is not based on the selection criteria for patients entering the study...We believe the authors were alluding to the post-study evaluations, which showed that almost all patients found that treatment with MS Contin more effectively controlled their pain. Therefore, the patients retrospectively expressed less satisfaction with their prior analgesic regimens...We propose to incorporate a statement to resolve you objection as follows: In some studies it is reported that all patients were dissatisfied with their analgesic regimens for reasons of inadequate pain relief or inconvenience of dosing interval or method.” “The third objection concerns the comparability of patients and whether preference was measure consistently across each study. The seven studies were under one or the other of the protocols attached...the patient selection criteria and the evaluation methods were essentially the same in both protocols. The global evaluations under both protocols measured effectiveness in pain relief, and the 	PDD8006000250

			<p>frequency and severity of side effects as compared with the prior analgesic regimens.”</p> <ul style="list-style-type: none"> • “A statement listing the adverse effects most commonly encountered in these studies will be featured, to provide fair balance in conformity with the April, 1994 guidance letter issued by DDMAC. This will be in addition to the warnings and statements of major hazards that were already prominently featured in the subject Booklet.” • Objection to the headline “‘For equal analgesia, compare the dosing schedules’ is misleading because it implies that the doses of the represented products are equipotent. The products are accurately represented as providing ‘approximately equivalent analgesia’, based upon the standard medical references which are recognized by expert medical opinion and approved by authoritative scientific bodies...the statement of equal or approximately equivalent analgesia between dosage units of the products represented is based upon substantial and adequate scientific evidence....To resolve the objection, the headline for the booklet chart will be: Each vertical column of tables or capsules provides approximately equivalent analgesia, according to standard equianalgesic dosage tables. ” 	
MS Contin	5/12/1994	From FDA	<p>FDA’s response to Purdue’s submission of revised promotional launch materials for MS Contin 200 mg submitted on 3/10/14 and 3/16/14. The FDA found the revised materials unacceptable.</p> <p>Overall Recommendation for All Proposed Letters</p> <ul style="list-style-type: none"> • Enlarge the size and prominence of the CII symbol. • “...revise the sentence discussing the use of regularly scheduled oral morphine to read: ‘Regularly scheduled administration of oral morphine to control advanced/chronic/moderate to severe pain in cancer patients...’ (emphasis added)” <p>Dear Pharmacist Letters Letters should be acceptable if the following</p>	PDD8006000213

			<p>revision is made:</p> <ul style="list-style-type: none"> Revise the last letter to say, “Please read the enclosed prescribing information and note that MS Contin 200 mg is intended for a small percentage (7-10%) of cancer patients. Since the 200 mg strength is likely to be toxic if prescribed or used in error, special care should be taken in stocking, filling, and re-filling prescriptions for this strength.” <p>Dear Hospice Director Letters Letters should be acceptable if the following revision is made:</p> <ul style="list-style-type: none"> Revise the last letter to say, “Please read the enclosed prescribing information carefully. As you can see, MS Contin 200 mg is intended for the 7-10% of patients who have high daily morphine demands. As with all high strength opioid products, care should be taken in the initiation and continuation of treatment with MS Contin 200 mg.” <p>Dear Oncology Nurse Revise the last sentence to be the same as listed in Dear Hospice Director.</p> <p>Dear Doctor Letters Letters should be acceptable if the following revision is made:</p> <ul style="list-style-type: none"> Revise the last sentence to say, “Please read the enclosed prescribing information carefully. As you can see, the 200 mg strength was developed to meet the clinical needs of the minority of patients who develop a high oral morphine demand. Because of its potential toxicity in non-opioid tolerant patients, care should be taken in the initial prescription and refill of prescriptions of this oncologic dosage form.” <p>Dear Medicaid Administrator Revise the last sentence to be the same as listed in Dear Hospice Director.</p> <p>Dear Pharmaceutical Wholesaler Revise the last sentence to be the same as listed in Dear Pharmacist.</p>	
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			<p>Dear Pharmaceutical Buyer Letter should be acceptable if the general comments related “to the size and prominence of the CII symbol and the addition of a clarifying term to the statement about use of regularly scheduled oral morphine are made.”</p> <p>Press Release Is acceptable provided the “general comments related to the size and prominence of the CII symbol and the addition of a clarifying term to the statement about use of regularly scheduled oral morphine are made.”</p> <p>Visual Aid Is unacceptable for the following reasons:</p> <ul style="list-style-type: none"> • “The statement ‘With no ceiling dose’ is misleading in isolation because it oversimplifies the appropriate and safe use of the 200 mg strength.” • “The headline: ‘When higher doses are necessary for increased pain’ paraphrases the indication for the MS Contin 200 mg strength and should be presented prominently at the opening of the visual aid.” DDMAC recommends that the headline be switched to the location where “Titrating upward can provide continuous pain control” is located. • “The bar graph is misleading because it overstates the potential patient population for MS Contin 200 mg. The approved labeling for MS Contin 200 mg states ‘The MS Contin 200 mg tablet is for use only in opioid tolerant patients requiring daily morphine in equivalent dosages of 400 mg or more.’ Therefore, the graph should be revised to emphasize the 7-10% of opioid tolerant patients who actually require greater than 400 mg of morphine per day.” • “The statement ‘200 mg MS Contin tablets are for use only in opioid tolerant patients’ should be more prominently displayed.” 	
MS Contin	5/18/1994	From FDA	FDA found the proposed combined advertisements for MS Contin 200 mg and the Partners Against Pain Campaign submitted on 5/9/1994 to be acceptable for use.	PDD8006000223
MS Contin	5/27/1994	To FDA	Purdue’s response to the FDA letter from 5/12/1994 with the recommendations for the proposed promotional materials for MS Contin 200 mg.	PDD8006000227

MS Contin	6/1/1994	To FDA	<p>Purdue submits a visual aid entitled “Clinically Effective-Cost Effective for review and comments.</p> <p>All Proposed Letters</p> <ul style="list-style-type: none"> • Purdue agrees to increase the size of the CII symbol. • Purdue disagrees with the recommendation to revise the sentence, “Regularly scheduled administration of oral morphine to control pain in cancer patients is recommended” by adding a limiting reference to “advanced” cancer. “Any statement suggesting that oral morphine in general, or 200 mg controlled-release tablets in particular, is for use only in ‘advanced’ disease would be false. The term ‘advanced cancer’ is generally understood to mean patients in the terminal stage of disease progression...The attitude that opioids are to be used only when the patient is terminal, is strongly criticized by the medical groups...There is no justification in the approved product labeling, or in medical practice for the proposed restriction to ‘advanced’ disease.” • The intended patient population is already boldly and prominently featured as follows: “‘MS Contin 200 mg Tablets are for use only in opioid tolerant patients requiring daily morphine equivalent dosages of 400 mg or more.’ This statement completely limits the use of this tablet strength as provided in the approved package insert for the product.” <p>Letters to Pharmacists</p> <ul style="list-style-type: none"> • Purdue agrees to incorporate the following sentence: “Please read the enclosed prescribing information carefully, and note that MS Contin 200 mg is for the 7-10% of patients with high daily opioid demands. As with all high strength opioid products, care should be taken in the dispensing of prescriptions for this strength.” • “We are concerned that the form of the various statements as recommended in your letter would infer that there is a higher professional standard, or even that a greater legal duty of care...” <p>All Letters and Press Release</p> <ul style="list-style-type: none"> • Purdue will incorporate the following 	PDD8006000457
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			<p>sentence in all their letters and the press release, as follows: “Please read the enclosed information carefully, and note that MS Contin 200 mg is for the 7-10% of patients with high daily opioid demands. As with all high strength opioid products, care should be taken in the initiation and continuation of treatment with this strength.”</p> <p>Visual Aid Purdue agrees to revise the aid to conform to all the changes recommended by DDMAC.</p>	
MS Contin	6/7/1994	From FDA	<p>Letter from the FDA to Purdue’s CEO regarding concerns about Purdue’s willingness to cooperate with DDMAC and to comply with the FDCA regulations.</p> <p>DDMAC is concerned specifically with regards to Purdue’s actions related to two misleading promotional items.</p> <p>1992 Brochure “There’s a Big Difference Between These Tablets” The brochure was allegedly provided to representatives during an Oncology Nursing Society Meeting. The brochure is misleading for the following reasons:</p> <ul style="list-style-type: none"> • “The brochure contains a number of statements that MS Contin is not therapeutically equivalent or bioequivalent to Oramorph SR. Specifically, the statement, ‘The FDA’s <u>Approved Drug Products with Therapeutic Equivalence Evaluations</u> (‘The Orange Book’) rates Oramorph ER as a ‘BC’ product-meaning that it is not considered to be therapeutically equivalent for generic substitutions with MS Contin Tablets’ was objected to in DDMAC’s October 15, 1993, Notice of Violation (NOV) letter to your firm.” • In Purdue’s response from December 8, 1993, it was stated that “When quoting or referring to the <u>Orange Book</u> listing of MS Contin in future MS Contin promotion, the statement will be substantially in the following form...’ (emphasis added): ‘...This rating applies to extended-release drugs for which no bioequivalence data have been submitted and, therefore, there is 	PDD8006000409

			<p>no known therapeutic equivalent to MS Contin Tablets.”</p> <ul style="list-style-type: none"> “...DDMAC did not intend for Purdue Frederick to continue to use the promotional brochure containing violative promotional messages for some indefinite period of time. It was our understanding that Purdue Frederick would revise its materials to incorporate the corrections agreed upon to resolve the objections raised in the NOV letter...Adequate time has elapsed for your firm to revise its promotional materials for MS Contin Tablets. “This brochure is misleading because it fails to provide any risk, warning, precaution or adverse effects information. This information is vital to the appropriate and safe use of MS Contin Tablets.” <p>DDMAC Recommendations</p> <ol style="list-style-type: none"> 1. Discontinue immediately the use of the brochure and any other items using the objectionable language 2. Provide a response to DDMAC with your intent to comply 3. Provide DDMAC with a copy of all correspondence to the promotional field force related to the above brochure 4. Provide in writing, a listing of all current labeling and advertising for MS Contin <p>“I regret having to send this letter to you, but I think it is important for you to know that we are seriously concerned about these issues. We recognize that you are involved in a highly competitive market, and that it is important to maintain a level playing field among competitors. We look forward to working with you and your firm to address these issues and to assure that the information disseminated in the promotion of these products is neither false nor misleading.”</p>	
MS Contin	6/8/1994	From FDA	FDA’s response to Purdue’s letter from 5/27/1994 with the proposed revisions to the promotional launch materials for MS Contin 200 mg. DDMAC finds the proposed intended actions to be acceptable.	PDD8006000234
MS Contin	6/15/1994	To FDA	<p>Purdue’s response to the FDA letter from 6/7/1994.</p> <p>“I find most distressing your statement that you ‘have become concerned about Purdue Frederick’s willingness to cooperate with DDMAC and to</p>	<p>PDD8006000416</p> <p>PDD8023022008</p>

			<p>comply with the Federal Food, Drug and Cosmetic Act, and the applicable regulations.’ I give you my personal assurance that there is no basis for such concern and that from the top down, our Company is committed to working cooperatively and constructively with you and all other Divisions of the Agency. I believe that the concern you expressed may be based on a misunderstanding, and I would hope that upon review of the documents you will agree that is what has occurred.”</p> <p>Regarding the brochure, Purdue believes that DDMAC’s “interpretation is the source of the misunderstanding. The NOV letter discussed only the Reprint Carrier...and did not refer to the Brochure...”</p> <p>Purdue included the brochure in the list of promotional materials it would continue to use in response to the NOV letter. DDMAC didn’t object thus Purdue understood the situation to be that they could use the brochure.</p> <p>Purdue makes the following observations:</p> <ul style="list-style-type: none"> • “The statement to which you object is factually true and accurate, as is the alternative statement suggested by DDMAC in the October 15, 1993 letter. I believe there is no material difference between the statement we first used...and the statement which DDMAC proposed as acceptable...While we think there are no material differences between these two statements, we agreed, in the spirit of cooperation, to use DDMAC’s preferred version in any future promotional pieces. WE have adhered to this commitment” <p>Purdue agrees to discontinue use of the piece immediately. “Your letter indicates that you regard as a part of your responsibilities the creation and maintenance of ‘a level playing field between companies with similar products.’ This is most important to us because the controversy between our Company and DDMAC arose out of what we came to regard as the inability or disinterest on the part of your predecessors to act against grossly false and misleading comparative promotions that have been distributed against our product, MS Contin Tablets, by Roxane Laboratories <u>for more than five years.</u>”</p>	
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MS Contin	6/17/1994	From FDA	<p>FDA’s response to Purdue’s 6/1/1994 submission of a visual aid entitled “Clinically Effective-Cost Effective”</p> <p>DDMAC objected to the use of the phrase “cost-effective.”</p> <ul style="list-style-type: none"> • “DDMAC interprets the phrase cost-effective’ as an implication of a conclusion from adequate and well-controlled studies of comparative products used in actual clinical practice with the definition and valuation of specific economic end-points.” <p>DDMAC objected to the use of comparative prices from the Red Book.</p>	PDD8006000457
MS Contin	6/27/1994	From FDA	<p>Letter from the FDA to Purdue regarding an investigation of a complaint about possible inappropriate promotional activities by a Purdue sales representative. “Specifically, DDMAC received a copy of a letter addressed to an oncologist at an institution which had recently switched from MS Contin to Oramorph SR. The letter appears to be an attempt to sway the oncologist to convince the Pharmacy and Therapeutics Committee to reverse its decision and to put MS Contin back on the formulary.”</p> <p>“DDMAC is concerned about the information disseminated in this particular communication. DDMAC previously informed Purdue Frederick</p>	PDD8006000425

			<p>that it objects to the use of FDA letters, or excerpts of letters out of context in promotional activities...In this instance, the statements excerpted from the Roxane NOV letter by this representative were taken out of context and misrepresent the full content of the letter.”</p> <p>“Second, DDMAC has advised Purdue Frederick about the use of bioequivalence data in an attempt to show a meaningful difference between MS Contin and Oramorph SR. Also, Purdue Frederick agreed on March 24, 1994, to not use data from the Bloomfield article in promotion until pharmacokinetic and clinical data has been submitted to the agency for review. As of this letter, these data have not been submitted.”</p> <p>Purdue was asked to respond and told to immediately discontinue the use of the Roxane NOV letter and bioequivalence data as promotional items.</p>	
MS Contin	6/30/1994	To FDA	<p>Purdue’s response to the FDA letter from 6/17/1994 concerning the visual aid entitled “Clinically Effective-Cost Effective.”</p> <p>MS Contin is “cost-effective”</p> <ul style="list-style-type: none"> Purdue argued that “[t]here is adequate, valid scientific evidence to substantiate that MS Contin is less costly, while achieving the therapeutic objective of relieving moderate to severe pain, in comparison with...the PCA pump.” <p>Red Book Price List</p> <ul style="list-style-type: none"> Purdue agreed that the “Red Book listing is not the only fair consideration in comparing prices. Total costs of using the alternate product must be considered, as well as discounted pricing generally available to hospitals and health maintenance organizations.” <p>Summary</p> <ul style="list-style-type: none"> Purdue argued that “the statement that MS Contin is cost-effective in the context of the subject visual aid is adequately substantiated and is neither false nor misleading.” 	PDD8006000462
MS Contin	7/1/1994	To FDA	<p>Purdue’s response to an FDA letter from 3/14/1994 requesting information about a letter sent by a sales representative to a medical center.</p>	PDD8023022258

			To correct the action Purdue would issue corrective letters to the physicians that received the original letter and issue a bulletin to all field representatives "reinforcing the procedures prohibiting the use of unapproved letters or materials in promotion."	
MS Contin	7/7/1994	From FDA	<p>FDA's response to Purdue's letter on 5/10/94 regarding the "Cancer Pain" booklet. "DDMAC has reviewed the responses and continues to object to the use of pooled data from the five separate studies that were submitted to support the claim of patient preference." DDMAC objected for the following reasons:</p> <ul style="list-style-type: none"> • Studies are all open-label and bias prone. "In fact, the question asked to the investigator is 'MS Contin is superior, better, same, inferior to the previous analgesic regimen?' By asking this leading question, the study has introduced an investigator bias. Furthermore, both protocols fail to mention that 'patient preference' is a primary study variable." • "The drug doses and dosing intervals under both protocols appear to be adjustable. Therefore, there is no mechanism to assure comparability of analgesic dosing between when the patient was taking MS Contin and when the patient was on their maintenance analgesic. This is important because the comparison of MS Contin to the previous maintenance analgesic is the basis for your superiority claim." • "The order of drug assignment is not balanced over time and is a fundamental flaw. Through randomization, half of the patients should have been assigned to receive MS Contin CR first. This balance is a basic feature of an adequate and well-controlled study designed to compare the effect of two different drugs using data collected on each drug in the same patient." • "MS Contin's superiority is claimed over a variety of competitor products. This claim is not valid because Purdue Frederick has failed to provide evidence in support of MS Contin's superiority over each competitor by a margin of 93 percent." <p>"Should Purdue Frederick consider revising the Cancer Booklet, the inclusion of references, as outlined in your May 10, 1994 response, for the equivalent analgesia chart would be acceptable."</p>	PDD8006000390

			However, continued use of pooled data from the seven studies to support a claim of patient preference for MS Contin would not be acceptable.”	
MS Contin	7/13/1994	From FDA	FDA’s response to Purdue’s 7/1/94 and 7/7/94 letters in response to the inquiries made by DDMAC regarding the promotional activities by their sales representative. No further action is required.	PDD8006000454
MS Contin	7/27/1994	From FDA	<p>FDA’s response to PPLP’s letter from 6/30/1994 responding to objections raised by DDMAC to the use of the term “cost-effective.”</p> <ul style="list-style-type: none"> • PPLP responded, “there is adequate valid scientific evidence to substantiate that MS Contin is less costly, while achieving the therapeutic objective of relieving moderate to severe pain, in comparison to the...PCA pump.” • FDA Response: Not persuaded by the argument. DDMAC agreed that MS Contin is effective in “achieving therapeutic objective of relieving moderate to severe pain.” However, this fact in association with the lower price isn’t adequate to substantiate a “cost-effectiveness” claim. The evidence may support a claim for “cost-minimization.” • If PPLP “has data from studies comparing MS Contin to other methods of pain management, such should be submitted to the agency for review.” 	PDD8006000480
MS Contin	8/12/1994	To FDA	<p>PPLP’s response to DDMAC’s letter dated 7/27/1994 on the “cost-effective” claim for MS Contin.</p> <ul style="list-style-type: none"> • PPLP recognizes that the DDMAC interprets the term “cost-effective” to be “a technical term of art in drug regulation.” DDMAC advised that “comparative cost-effectiveness (CE) claims may be supported only by comparative studies with ‘outcome data’ determining the ‘many variables that can affect relative cost among competing therapies.’ PPLP wonders if there are any examples of competing therapies that meet these standards. • PPLP believes “that the developing policy of DDMAC to regulate CE claims should fairly consider the adequacy of the available scientific evidence, including the opinion of qualified experts, and then determine whether comparative studies under novel 	PDD8006000487

			<p>pharmacoeconomic protocols are required to resolve any undetermined issues.”</p> <ul style="list-style-type: none"> • PPLP wants to use the statement “the oral route is the preferred route of analgesic administration because it is the most convenient and cost-effective.” • However, while PPLP contends that the “cost-effective” claim is supported by evidence they discontinued use of the subject promotional visual aid. In the future they will use the term “cost-minimization.” 	
MS Contin	9/6/1994	From FDA	<p>FDA acknowledges receipt of 8/12/1994 response from PPLP.</p> <ul style="list-style-type: none"> • DDMAC objects to PPLP’s wish to use the statement, “the oral route is the preferred route of analgesic administration because it is the most convenient and cost-effective,” because the “statement may not necessarily be based on data derived from adequate and well-controlled comparative studies.” • DDMAC takes the position that “any statement or claim that a product or route of administration is cost-effective, when used in promotion, must be supported by comparative studies.” • DDMAC will consider use of this statement to be false or misleading promotion “unless it is substantiated by data from adequate and well-controlled studies.” 	PDD8006000491
MS Contin	9/12/1994	To FDA	Purdue submits a Dear Doctor and Dear Pharmacist letter for review and comments.	PDD8006000494
MS Contin	9/13/1994	Meeting with FDA	<p>Memo with notes from meeting with the FDA. Curtis Wright from the FDA gave his opinions on some Purdue overheads.</p> <p>“The opioid to start with”</p> <ul style="list-style-type: none"> • Wright “stated that there were some problems in switching patients from previous opioid regimens directly to OxyContin...Curtis indicated a desire to include language in our patient insert which recommends initiating immediate-release oxycodone before starting with OxyContin. As a result, he feels that the above claim may be problematic.” • “As you know, this claim is essential to the present positioning of OxyContin. We must be sure to overcome this problem, since it will have a major impact on our entire marketing platform.” 	PKY181714098

			<p>“Short Elimination Half-Life”</p> <ul style="list-style-type: none"> Wright “indicated that this language must be qualified by stating that OxyContin attains steady-state blood levels within 24 to 36 hours.” <p>“Second Generation Contin Delivery System”</p> <ul style="list-style-type: none"> “...this implies a new and improved delivery system...if we qualify this claim by showing how the combination of oxycodone and this new Contin delivery system allow for more predictable relationships between dose, concentration, and pain relief, thereby leading to more consistent q12h dosing, it will be okay.” “If FDA would not allow us to state the fact that this is a second generation delivery system, I think we would have recourse. Obviously, this is a fact which cannot be disputed and is a feature of OxyContin. It does not necessarily imply that this delivery system is new and improved. However, Dr. Wright’s suggestion that we qualify this, by showing how pk/pd data is improved over MS CONTIN, makes a very nice selling story explaining why OxyContin is a better choice than MS CONTIN.” <p>“Most Efficiently Titrable Opioid”</p> <ul style="list-style-type: none"> “...this will need further validation from a comparison of our well-controlled clinical trials and the MS CONTIN clinical trials. The project team realized that this would require more time to massage the data. This claim may not be available at the time of launch.” <p>“Preferred by Patients over Pre-Study Opioids”</p> <ul style="list-style-type: none"> “...this claim may be too broad even if the protocols asked patients to rate OxyContin versus their pre-study opioid. He indicated that just because they prefer the q12h dosing schedule it does not necessarily allow for a patient preference claim.” “I do not want to back down from making these claims for OxyContin. They can be very convincing when selling a physician on switching from other opioids. This is an issue we should push with them.” 	
MS Contin	9/16/1994	To FDA	Letter from Purdue’s attorneys to the FDA advising them of promotional actions by Roxane	PDD8023023195

			Laboratories for their product Oramorph SR that Purdue believes are misleading.	
MS Contin	9/21/1994	To FDA	Another letter from Purdue's attorneys to the FDA advising them of promotional actions by Roxane Laboratories for their product Oramorph SR that Purdue believes are misleading.	PDD8023023209
MS Contin	10/3/1994	From FDA	FDA's response to PPLP's 9/12/1994 submission of a Dear Doctor and Dear Pharmacist letter. <ul style="list-style-type: none"> “DDMAC objects to the statements ‘Clinical experience with MS Contin Tablets is well documented in scores of published studies involving thousands of patients’ and ‘MS Contin are the most widely studied, <u>controlled-release</u> strong opioid’ because they imply superior safety and efficacy as compared to Oramorph SR.” DDMAC's position is that “it is misleading to suggest superiority of a drug based solely on a greater number of references for one drug over the other.” 	PDD8006000494
MS Contin	10/13/1994	To FDA	PPLP's response to the FDA's letter from 10/3/1994. <ul style="list-style-type: none"> PPLP does not agree that the statements are false and misleading. “These statements are simply true declarations of fact. They mean that MS Contin Tablets have been thoroughly studied and characterized. We regard this as appropriate, useful information for physicians and pharmacists.” PPLP revised the letters with the new statement, “the clinical properties of MS Contin Tablets are well-characterized in scores of published studies involving thousands of patients.” 	PDD8006000499
MS Contin	12/20/1994	To FDA	Letter to the FDA advising them of patient preference claims made... Reference is made to the 3/25/1994 letter from the FDA regarding the “Cancer Pain” booklet in which the FDA objected to a patient preference study favoring MS Contin over prior analgesic regimens.	PDD8006000395
MS Contin	2/8/1995	From FDA	Letter re: Cancer Pain Management materials MACMIS ID 2299 Direct-to-consumer campaign	Bates Unavailable
MS Contin	2/10/1995	To FDA	Purdue agrees to adopt the changes recommended by the FDA in their letter dated 2/8/1995 regarding the Cancer Pain Management materials. <p>Purdue asks for reconsideration of the proposed revision to use the word “may” in the title, “Cancer pain can be controlled.” “The word ‘can’ in this context does not imply a guarantee that all cancer</p>	PDD9316711959

			<p>pain is controllable...We agree that in this context the word 'can' more strongly expresses the possibility of pain control than 'may.' This is fully justified by the fact that cancer pain <u>is</u> controllable in most cancer patients."</p> <p>"Our Cancer Pain Management program targets the problem of undertreatment of cancer pain...No consumer or patient will be misled by the title statement we have proposed."</p>	
MS Contin	12/4/1996	From FDA	Letter from the FDA to Purdue regarding their 11/26/1996 response to the 11/20/1996 Warning Letter. "In your letter, you indicated that the dissemination of the promotional materials that were the subject of the Warning Letter has been suspended. We note that although these specific materials were referenced in the Warning Letter, the letter addresses all materials that contain claims of product superiority that are not supported by substantial evidence.	PDD8006000540
MS Contin	12/13/1996	To FDA	Purdue submits a list of all promotional materials for MS Contin currently in use as requested in the 11/20/1996 Warning Letter.	PDD8006000566
MS Contin	1/14/1997	To FDA	Purdue submits additional samples of promotional materials listed in the Schedule provided to the FDA in the 12/13/1996 submission.	PDD8006000566
MS Contin	1/15/1997	From FDA	Contents Not Reported	Bates Unavailable
MS Contin	1/30/1997	To FDA	Purdue submits a copy of a paper entitled: Lazarus, et al, A Multi-Investigator Clinical Evaluation of Oral Controlled-Release Morphine (MS Contin Tablets) Administered to Cancer Patients, The Hospice Journal, Vol. 6(4) 1990 per the FDA's request.	PDD8023031260
MS Contin	3/5/1997	To FDA	Contents Not Reported	Bates Unavailable
MS Contin	3/14/1997	To FDA	<p>PPLP sends the FDA an affidavit and CV from Dr. C. Stratton Hill, Jr. PPLP submits that "his opinions are entitled to great evidentiary weight in this matter, as we believe they represent the general view of health care professionals in this field..."</p> <p>"this use of the DDMAC Warning Letter to support false and misleading claims and comparisons of Oramorph SR to MS Contin makes it more difficult to reach an accord with your office in resolving the issues raised in the Warning Letter."</p>	PDD8023031290

MS Contin	4/3/1997	To FDA	PPLP encloses a draft letter to send to health care professionals who may have received a presentation on the promotional materials in question. The draft was derived from the draft the FDA provided on 1/15/1997.	PDD8023031305
MS Contin	4/23/1997	Meeting with FDA	Contents Not Reported	Bates Unavailable
MS Contin	4/30/17	To FDA	Contents Not Reported	Bates Unavailable
MS Contin	5/1/1997	To FDA	Letter from Law firm	Bates Unavailable
MS Contin	5/3/1997	From FDA	<p>FDA's response to PPLP's submission from 12/13/1996 with the copies of all promotional materials in use following the Warning Letter. Following review of the material, DDMAC had two concerns with the materials.</p> <ul style="list-style-type: none"> Purdue's suggestion that the use of MS Contin improves quality of life is not supported and thus the claims are false and/or misleading. "To support quality of life improvement claims, the company should submit evidence of validity of the measurement scales used and the adequacy and rigor of the studies used to support these claims. Such evidence should document the validity, reliability, sensitivity, responsiveness, and clinical meaningfulness of the measurement scale in patients with the disease or condition under study. The measurement scale submitted to substantiate Purdue's quality of life claims does not satisfy these criteria." "DDMAC is also concerned by Purdue's lack of adequate fair balance in some of the promotional materials submitted." One of the brochures "fails to provide reasonably comparable prominence for the fair balance information...As submitted, DDMAC considers this promotional item to be lacking in fair balance or otherwise misleading." 	PDD8006000575
MS Contin	5/19/1997	To FDA	<p>Purdue's response to the FDA's letter from 5/3/1997 with comments on MS Contin promotional materials.</p> <p>Quality of Life Claims</p> <ul style="list-style-type: none"> "In our opinion, the materials to which your letter refers give proper weight and credence to the evaluation of patients with 	PDD8023114266

			<p>chronic moderate to severe pain, as to the effects of treatment and relief of pain on their daily functional abilities and relationships, hence 'quality of life.' We submit that this is useful information to share with caregivers responsible for the treatment and management of patients with debilitating pain, and such information should not be barred by artificially stringent standards of clinical proof."</p> <ul style="list-style-type: none"> Purdue argued that the statements in question were supported by substantial scientific evidence and weren't misleading. <p>Lacking in Fair Balance</p> <ul style="list-style-type: none"> "We believe that the information as presented on the flap and back cover (including reference to the enclosed full disclosure information) fully meets regulatory standards. However, to avoid dispute we have discontinued the dissemination...and our representatives are being notified to destroy any copies remaining in the field." 	
MS Contin	5/21/1997	From FDA	<p>FDA's response to PPLP's submission from 4/30/1997 of the Dear Health Care Professional letter "in proposed fulfillment of DDMAC's request that Purdue Frederick issue a corrective letter to recipients of unlawful promotional material..."</p> <ul style="list-style-type: none"> DDMAC reviewed the letter and found it "unacceptable because the letter would not be likely to correct the false and misleading messages that Purdue Frederick disseminated, as described in our November warning letter. The letter should, at a minimum, explain in clear and unequivocal terms that MS Contin has not been shown to be better than any other long narcotic therapy for cancer pain." DDMAC does not agree with Mr. Kaplan's assertion in his 5/1/1997 letter "that 21 C.F.R. §200.5 does not compel us to require a legend on the envelope of the proposed DHCP letter." DDMAC was concerned that no DHCP letter has been issued yet as requested in their November 1996 Warning Letter. "Purdue Frederick continues to fail to recognize its violative actions and the need for corrective action. This failure has 	PDD8023031317

			<p>resulted in an unacceptable delay in correcting Purdue Frederick's violative messages. Accordingly, DDMAC is considering other options that may be appropriate in this matter, including dissemination by DDMAC of an appropriate corrective message about MS Contin."</p> <ul style="list-style-type: none"> If DDMAC doesn't receive a written plan by PPLP by 5/20/1997 with a mutually accepted DHCP letter, DDMAC will assume PPLP has decided not to participate "in the preparation and dissemination of the corrective message." 	
MS Contin	5/27/1997	Meeting with FDA	Contents Not Reported	Bates Unavailable
MS Contin	5/30/1997	To FDA	<p>Purdue's letter notifying the FDA that the envelope and letter of the DHCP letter will bear the notice "IMPORTANT CORRECTION OF DRUG INFORMATION."</p> <p>Purdue repeats their "firm conviction that the Levy reprint and booklet version contain fair, balanced and useful information about all of the pharmacologic choices for the treatment of patients suffering with cancer pain, and it is a loss to professionals and patients alike to stop the dissemination of this valuable educational article."</p> <p>Purdue will mail the DHCP letter to oncologists, radiation oncologists, oncology/hospice nurses, consultant pharmacists, and hospice pharmacists.</p>	PDD8023114274
MS Contin	6/3/1997	To FDA	Contents Not Reported	Bates Unavailable
MS Contin	6/6/1997	From FDA	<p>DDMAC finds the revised DHCP letter acceptable and agrees to the proposal for dissemination.</p> <p>In response to PPLP's comments from the 5/20/1997 article, the "FDA favors dissemination of truthful, nonmisleading, and balanced information about the benefits and risks of prescription drugs. However, we note that although the Levy article contained useful information about the treatment of pain, it also contained unsubstantiated promotional statements that favored Purdue Frederick's product over competitive products. In preparing the materials that it derived from Dr. Levy's article and that it disseminated in the sale and promotion of MS Contin, Purdue Frederick had the opportunity to</p>	PDD8023114262

			exclude the promotional claims, but failed to do so.”	
MS Contin	2/16/1999	To FDA	Submission of MS Contin Myths about Opioids for review	PDD8023032821
MS Contin	3/17/1999	To FDA	Letter from Purdue to the FDA advising that they mailed out an announcement sheet and letter to pharmacists that enclosed the package insert for OxyContin rather than MS Contin. To correct the problem a second mailing was issued.	PDD8023032838
MS Contin	3/24/1999	To FDA	Submission of MS Contin Dispense As Written Visual Aid for review	PDD8023032852
MS Contin	5/3/1999	To FDA	Submission of MS Contin Low Back Pain/Neck Pain “Pain State” Precise Letter-to increase awareness of using opioids to treat back/neck pain for review	PDD8023032942
MS Contin	5/11/1999	To FDA	Submission of MS Contin MD/Pharmacist Audiotape on Pain Management, and Product Data Brochure for review	PDD8023035102
MS Contin	6/8/1999	To FDA	Submission of MS Contin General Benefits Precise Letter-follow-up to sales calls for review	PDD8023038094
MS Contin	6/17/1999	To FDA	Submission of MS Contin Pain Evaluation Flow Sheet and “Dispense as Written” Quest Letter – Direct Mail Follow-up letter for review	PDD8023044462
MS Contin	7/2/1999	To FDA	Submission of MS Contin Professional Print, “Principles of Pain Management Module Two – Pharmaceutical Management of Pain” for review	PDD8023045826
MS Contin	8/2/1999	To FDA	Submission of MS Contin Reorder Agency for Health Care Policy and Research “Main Book” entitled “Management of Cancer Pain” for review	PDD8023046811
MS Contin	1/14/2000	To FDA	Submission of MS Contin Retail Announcement Letter, Sell-Sheet, Rebate Program #4 for review	PDD8023051546
MS Contin	5/10/2000	To FDA	Submission of the following MS Contin promotional materials for review: Rebate Wholesale Envelope, Rebate Retain Announcement Letter	PDD8023051937
MS Contin	10/27/2000	To FDA	Submission of MS Contin Professional Sales Aid Titration Guideline, MSIR labeling for review	PDD8023055672
MS Contin	3/20/2001	To FDA	Submission of Dispelling the Myths About Opioids for review	PDD8023055742
MS Contin	11/9/2001	To FDA	Submission of MS Contin ID Pill Card	PDD8023086542
MS Contin	6/12/2002	To FDA	Submission of MS Contin rebate announcement letter, rebate retail sell letter, wholesale sell sheet, rebate wholesaler announcement letter	PDD8023087212
MS Contin	4/1/2003	To FDA	Submission of Retailer Rebate Sell Sheet, Announcement Letter, and envelope for review	PDD8023092680
MS Contin	3/15/2004	To FDA	Submission of the following promotional items for review: Purdue Letter 2/17/94 to “Pharmaceutical Buyer” Regarding Correction of a Packaging Label to Reflect Purdue’s Address Change, wholesaler pricing schedule	PDD8023100803
MS Contin	4/21/2004	To FDA	Submission of the following promotional items for	PDD8023100832

			review: 2004 Pain Management Prescribing Guide, wholesaler pricing schedule	
MS Contin	8/23/2004	To FDA	Submission of the following promotional items for review: Wholesaler Sell Sheet, Pricing Schedule, Package Insert	PDD8023101508
MS Contin	3/11/2005	To FDA	Submission of the following promotional items for review: Department of Veterans Affairs Authorized Federal Supply Schedule Pricelist, Package Insert, wholesaler pricing schedule	PDD8023101677
MS Contin	5/9/2005	To FDA	Submission of the following promotional items for review: MS Contin NDC Change Letter to Direct Buying Accounts, Package Insert, wholesaler pricing schedule	PDD8023101827
MS Contin	9/15/2005	To FDA	Submission of the following promotional items for review: Small but Important Changes to www.purduepharma.com to Reflect Recent Company Developments, Vermont Pricing Sheet, wholesaler pricing schedule	PDD8023105924
MS Contin	10/27/2005	To FDA	Submission of the following promotional items for review: Coupon Book, wholesaler pricing schedule	PDD8023106127
MS Contin	12/20/2005	To FDA	Submission of the following promotional items for review: 2005 Pain Prescribing Guide, Revised Vermont Forms – MS Contin, wholesaler pricing schedule	PDD8023106187
MS Contin	3/8/2006	To FDA	Submission of the following promotional items for review: Update Wholesaler/Chain Hospital, Hospital/Govt Hospital, Puerto Rico Wholesaler, Puerto Rico Chain pricing schedules	PDD8023106247
MS Contin	3/21/2006	To FDA	Submission of the following promotional items for review: Update MS Contin Pricing Disclosure Information for VT Prescribers, wholesaler pricing schedule	PDD8023106305
MS Contin	4/21/2006	To FDA	Submission of the following promotional items for review: An Info Alert for Pharmacist and Pharmacy Buyers to Announce the Introduction of Morphine Sulfate CR Tablets to Watson's Portfolio of Generic Products, Sample Representation of Watson Pharma's Letters to Contract Companies Offering Prices and Incentives for Morphine Sulfate CR Tablets	PDD8023106373
MS Contin	6/8/2006	To FDA	Submission of the following promotional items for review: MS Contin Updated Pricing Disclosure Information for Vermont Prescribers	PDD8023106407
MS Contin	8/17/2006	To FDA	Submission of the following promotional items for review: Watson Pharmaceuticals One Page Convention Panel for Oxycodone Controlled Release Tablets and Morphine Controlled Release Tablets	PDD8023113635
MS Contin	9/22/2006	To FDA	Submission of the following promotional items for review: MS Contin Vermont Pricing Disclosure Forms	PDD8023113843

MS Contin	12/21/2006	To FDA	Submission of the following promotional items for review: MS Contin Updated Pricing Disclosure Information for Vermont Prescribers	PDD8023113857
MS Contin	3/28/2007	To FDA	Submission of the following promotional items for review: MS Contin Vermont Pricing Disclosure Forms	PDD8023113913
MS Contin	7/12/2007	To FDA	Submission of the following promotional items for review: Information for VT Prescribers – MS Contin	PDD8023114295
MS Contin	8/29/2007	To FDA	Submission of the following promotional items for review: PAP Letter to Accompany PAP058-APS “Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain” 5 th Edition, Customized Letter to accompany APS Booklet (PAP058) request from University of Maryland School of Pharmacy, Letter to Advise Accounts both Direct and Indirect of Correct Company Name of our Products	PDD8023115463
MS Contin	11/5/2007	To FDA	Submission of the following promotional items for review: Vermont Pricing Disclosure Forms, MS Contin HCP Letter, MS Contin Revised HCP Letter	PDD8023115517
MS Contin	1/10/2008	To FDA	Submission of the following promotional items for review: Vermont Pricing Disclosure Forms	PDD8023115550
MS Contin	4/8/2008	To FDA	Submission of the following promotional items for review: Product Pictures for Red Book, Revision of Federal Supply Schedule for Purdue Pharma LP, Article of Pathways – American Society for Pain Management Nursing Newsletter, Information for Vermont Prescribers	PDD8023115630
MS Contin	5/9/2008	To FDA	Submission of the following promotional items for review: Update Wholesaler-Chain, Hospital-Govt Hospital, Puerto Rico Wholesaler-Chain pricing to reflect price increases 4/1/08	PDD8023115654
MS Contin	7/18/2008	To FDA	Submission of the following promotional items for review: Vermont Pricing Disclosure Forms	PDD8023115821
MS Contin	12/8/2008	To FDA	Submission of the following promotional items for review: Price Increase for Wholesalers, Hospital/Govt Hospital, Puerto Rico Wholesalers/Chains Effective 12/1/8, Update Rx Products Section of Purdue Website	PDD8023115718
MS Contin	2/20/2009	To FDA	Submission of Hospice Rebate Agreement to include increased rebates on MS Contin Tablets effective 1/1/09	PDD8023115811

Warning Letters

PURDUE			
Product	Date	Contents	BATES
OxyContin	5/11/2000	<p>Regarding journal advertisement entitled, “Proven Effective in Arthritis Pain” in the May 4, 2010 issue of the <i>New England Journal of Medicine</i>.</p> <p>Misleading Efficacy Presentation The presentation “suggests that OxyContin has been studied in all types of arthritis and can be used as first-line therapy for the treatment of osteoarthritis. However, this suggestion is unsubstantiated and lacks important information about the study.”</p> <ul style="list-style-type: none"> • The ad is “misleading because it suggests that OxyContin can be used as first-line therapy for the treatment of arthritis when such has not been demonstrated by substantial evidence.” • The ad is also “misleading because it does not prominently present the important contextual information that the inclusion criteria for the study were patients who were judged as having inadequate pain control with prn opioids and maximal NSAID therapy.” <p>The suggestion “that any dose of OxyContin can be used in the treatment of moderate to severe osteoarthritis pain is unsubstantiated, and consequently, misleading.”</p> <p>Misleading Safety Presentation “The Warnings section of the PI states that, ‘Respiratory depression occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration. This risk is not presented in your journal ad. Therefore, the suggestion that OxyContin can be used in the elderly without prominent disclosure of the above risk information is misleading.’”</p> <p>Conclusion and Requested Actions Immediately discontinue the use of the journal advertisement and all other promotional materials that contain the same or similar claims. Submit a written response describing intent and plans to comply.</p>	
OxyContin	5/15/2000	<p>Regarding journal advertisement entitled, “Proven Effective in Arthritis Pain” in the May 4, 2010 issue of the <i>New England Journal of Medicine</i>.</p> <p>FDA changed their opinion regarding the following claims and presentations in the journal advertisement.</p> <p>Misleading Efficacy Presentation “You present the headline ‘Proven Effective in Arthritis Pain...’ followed by selective results of a study conducted in 133 patients with moderate to severe osteoarthritis...However, your</p>	

		<p>presentation only highlights the most favorable results of the study and fails to present the results that were not as favorable...Therefore, your journal ad is misleading because you selectively present the study's most favorable results, without also prominently disclosing the results that were not as favorable"</p> <p>"Your presentation of the study results is misleading because you fail to include adequate context for the results that you present...Therefore, your journal ad is misleading, because you present the favorable conclusions from a study in the absence of qualifying contextual information concerning the study's limitations."</p>	
OxyContin	12/24/2002	<p>Regarding the journal advertisements on October 2, 2002 and November 13, 2002 that appeared in the <i>Journal of the American Medical Association</i>.</p> <p>"Your journal advertisements omit and minimize the serious safety risks associated with OxyContin, and promote it for uses beyond which have been proven safe and effective. Specifically, your advertisements fail to present in the body of the advertisements <u>any</u> information from the boxed warning in the approved product labeling (PI) for OxyContin regarding the potentially fatal risks associated with the use of OxyContin and the abuse liability of OxyContin...and make unsubstantiated efficacy claims promoting the use of OxyContin for pain relief. Your journal advertisements also understate the minimal safety information that is presented."</p> <p>"Your advertisements thus grossly overstate the safety profile of OxyContin by not referring in the body of the advertisements to serious, potentially fatal risks associated with OxyContin, thereby potentially leading to prescribing of the product based on inadequate consideration of risk. In addition, your journal advertisements fail to present in the body of the advertisements critical information regarding limitations on the indicated use of OxyContin, thereby promoting OxyContin for a much broader range of patients with pain than are appropriate for the drug. The combination in these advertisements of suggesting such a broad use of this drug to treat pain without disclosing the potential for abuse with the drug and the serious, potentially fatal risks associated with its use, is especially egregious and alarming in its potential impact on the public health."</p> <p>Lack of Important Risk Information</p> <p>"Your journal articles are misleading because they make prominent claims of effectiveness for pain relief, but omit from the body of the advertisements crucial facts related to the serious, potentially fatal safety risks associated with the use of OxyContin, the potential for OxyContin to be abused, and the limitations on its appropriate indicated use."</p>	

Omission of Material Facts Related to Abuse Liability and Fatal Risks

- “The principal message of both ads appears to be that OxyContin offers effective pain relief and has convenient dosing.”
- “These ad presentations, however, fail to present in the body of the advertisements critical safety information related to the use of OxyContin needed to balance these broad claims promoting its efficacy for pain relief. Neither one of your ads presents in the body of the advertisements any information from the boxed warning discussing OxyContin’s potential for abuse and the related considerations when prescribing the drug.
- Neither one of your ads presents in the body of the advertisements any information from the boxed warning disclosing that the drug can be fatal if taken by certain patients or under certain conditions.”
- “These ad presentations are accompanied by a brief summary of the prescribing information for OxyContin, including the boxed warning, and the ads include a reference to the brief summary. However, presenting important risk information in this manner is not in accordance with FDA’s prescription drug advertising regulations.”

Minimization of Risk in Information Presented

- “Your ads not only omit these important risks, but also understate the minimal safety information that you do disclose in the body of the advertisements, thus completely misrepresenting the safety profile of the drug. Your ads state that ‘The most serious risk with opioids, including OxyContin, is respiratory depression.’ This statement suggest that there are no specific safety considerations for OxyContin related to respiratory depression, which is false or misleading and could lead to prescribing of the product based on inadequate consideration of risk...It is especially troubling that your ads tout the dosing convenience of OxyContin as a benefit, but fail to warn of these associated serious safety risks that come from its controlled-release formulation.”
- “Your advertisements, in this context, also minimize the most common adverse events associated with OxyContin by describing ‘Common opioid side effects’ rather than side effects and safety risks that have been seen with OxyContin itself...By essentially suggesting that no safety or tolerability issues have been seen specifically with OxyContin, and by implying that OxyContin therapy is not associated with the serious and significant risks outlined above, your advertisements grossly misrepresent the safety profile of OxyContin. This is false or misleading and raises significant public health safety concerns.”

		<p><i>Overbroadening of Indication</i></p> <ul style="list-style-type: none"> • “Your advertisements suggest that OxyContin can be used in a much broader range of pain patients than has been proven to be safe and effective. This is even more problematic from a public health perspective given the serious safety risks associated with the drug and the serious deficiencies in the safety information presented in your advertisements.” • “These presentations are insufficient to give appropriate context and balance to your claims broadly promoting the use of this drug for pain relief...Therefore your advertisements fail to adequately communicate the actual indication for OxyContin and suggest its use for pain relief in a much broader range of patients than indicated.” • “In addition, your advertisements fail to present in the body of the advertisements the other important limitations on the indicated use of OxyContin...Although you prominently claim effective ‘relief’ and that the product ‘works,’ you fail to qualify that, as per the boxed warning, OxyContin is not intended to be used as a prn (as needed) analgesic.” • “Also, of concern, your advertisements,...represent the dosing convenience of OxyContin by showing dosage cups of the type used to dispense medication in a hospital setting, along with your broad claims of efficacy. The body of the advertisements, however, fails to present the important limitations on the use of OxyContin restricting it to certain hospitalized patients, as described in the OxyContin PI... You fail to present in the body of your advertisements any of these important limitations, thus suggesting the use of OxyContin in inappropriate patients.” <p>Conclusions and Requested Actions</p> <p>“Because of the significant public health and safety concerns raised by your advertisements, we request that you provide a detailed response to the issues raised in this Warning Letter. This response should contain an action plan that includes: immediately ceasing the dissemination of these advertisements and all other promotional materials that contain the same or similar violations outlined in this letter; providing a plan of action to disseminate accurate and complete information to the audience(s) that received the misleading messages; a written statement of your intent to comply with ‘1’ and ‘2’ above.”</p>	
OxyContin	1/17/2003	Same language as the 12/24/2002 Warning Letter	

Company Responses to Warning Letters

PURDUE			
Product	Date	Contents	BATES
OxyContin	5/25/2000	<p>Purdue's response to the FDA letters on 5/11/2000 and 5/15/2000 on the journal advertisement entitled "Proven Effective in Arthritis Pain" from the 5/4/2000 issue of the <i>New England Journal of Medicine</i>.</p> <ul style="list-style-type: none"> May 11, 2000 letter – company is agreeable to taking into consideration the FDA's comments, but it is their belief that the advertisement does provide the information required for a physician to prescribe the drug safely and to use it effectively. May 15, 2000 letter – would prefer a better-defined process for the FDA changing their opinion, they will follow their views in any new promotional description of the clinical study. Further publications of the advertisement were cancelled immediately upon receipt of the 5/11/2000 letter and no other promotional materials currently feature this clinical study. 	PURCHI-000701971
OxyContin	1/13/2003	<p>Purdue's response to the FDA warning letter from 12/24/2003 regarding the journal advertisements on October 2, 2002 and November 13, 2002 that appeared in the <i>Journal of the American Medical Association</i>. "Through this submission, we hope that the agency will be better able to understand the rationale behind Purdue's recent ads, and will appreciate that the differences between the agency's approach and Purdue's approach were the result of a misunderstanding, rather than intentional departure by Purdue from the understandings reached concerning OxyContin advertising during 2001."</p> <p><i>"There is no general prohibition on reliance on cross-reference to a boxed warning appearing the brief summary portion of an advertisement."</i></p> <ul style="list-style-type: none"> "....it can reasonably be concluded that the presentation of an appropriate 'brief summary' in a print advertisement, in conjunction with prominent cross-reference thereto elsewhere in the ad, would comply with the disclosure requirements and that a separate 'major statement' would be unnecessary for a print ad containing such a prominently referenced brief summary." <p><i>"Purdue's ads comply with FDA regulations and interpretations by providing textual information pertaining to side effects and risks and by prominently directing the reader to the boxed warning information in the brief summary portion of the ad."</i></p> <ul style="list-style-type: none"> "Both of Purdue's ads include a prominent reference in the body of the ad to the fact that there is a boxed warning and that it is presented in the adjacent brief summary portion of the ad...In addition, the body of the 	PURCHI-000711057

		<p>ads also prominently highlights the fact that the product can cause respiratory depression. This is <i>the</i> essential, inherent risk associated with the use <i>or</i> abuse of opioid products such as OxyContin and is, indeed, the risk that underlies essentially all of the risk information contained in the boxed warning.”</p> <ul style="list-style-type: none"> • “We still do not understand DDMAC to be advising that it is necessary to present <i>all</i> of the information in the boxed warning twice, or to present it in a box in the body of the advertisements. What we now understand, however, is that the agency believes that some additional information contained in the boxed warning should also be repeated in the body of the ad.” • “In short, Purdue is not interested in minimizing or obfuscating the risk information about its products. This information, however, is properly ‘balanced’ with truthful and non-misleading information about the importance of effective pain management and the valuable role that OxyContin can play in fulfilling that need.” <p><i>“No feature of the recent Purdue ads, taken individually or in context, implies or suggests usage of the product beyond the parameters of the approved indication or otherwise misstates or minimizes the limitations or risks of the product.”</i></p> <ul style="list-style-type: none"> • “Given the long-standing acceptance and repeated use of these various concepts in OxyContin promotion in various contexts both before and after adoption of the boxed warning, we seen no basis to treat the potential change in the agency’s position on these matters as exempt from the reasonable notice requirement of this regulation.” <p><i>“Correspondence and meetings between Purdue and FDA regarding promotional materials to be used subsequent to adoption of the boxed warning statement were honestly believed by Purdue to be consistent with the approach taken in its recent ads.”</i></p> <ul style="list-style-type: none"> • “Purdue now understands that the agency believes that some additional balancing/risk information should be duplicated and highlighted in these advertisements outside of the brief summary presentation. It has committed to do so and has withdrawn all possible pending advertisements until it is assured that they fully meet the agency’s requirements.” <p><i>“A Warning Letter is Unwarranted”</i></p> <ul style="list-style-type: none"> • “...Purdue firmly believes that its recent journal ads for OxyContin comply with the agency’s regulations governing professional ads and caused no confusion among healthcare professionals, particularly in light of 	
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		<p>Purdue's extensive informational campaign and the widespread publicity concerning OxyContin and its abuse liability. Nevertheless, Purdue has committed to voluntarily complying with the agency's requirements as they were explained to Purdue at our meeting. For these reasons, there is no need to issue official correspondence in this matter."</p> <ul style="list-style-type: none"> • "If the agency deems it necessary to document its position in writing, Purdue urges the agency to consider expressing its views succinctly, using clear, simple language, without any unnecessary verbiage that could be misconstrued and have unintended punitive consequences. Most importantly, it would be completely inappropriate under these circumstances for a letter to include language suggesting deliberate or reckless intent on the part of Purdue to violate FDA policies or regulations or speculating one way or another about the public health significance of the manner in which the information presented in the ads was formatted. 	
OxyContin	1/24/2003	<p>Purdue's response to the FDA warning letter from 1/17/2003 regarding the journal advertisements on October 2, 2002 and November 13, 2002 that appeared in the <i>Journal of the American Medical Association</i>.</p> <p>Overall Response</p> <ul style="list-style-type: none"> • Purdue believes "that these two new advertisements...are fair and accurate and in compliance with applicable law and regulations. Nevertheless, we will, of course, comply with the changes you seek." • Purdue strongly disagrees that the advertisements violate the Federal Food, Drug, and Cosmetic Act. "The Warning Letter does not state that the advertisements contain any untrue statement or fail to contain within the entire advertisement all required information about OxyContin...With all due respect, the placement used by Purdue is consistent with FDA's requirements as the agency has previously interpreted and applied them to journal advertisements for Purdue and other drug manufacturers." • Purdue also strongly disagreed that the advertisements would have any negative impact on the public health. "In addition to the points made above, the ads are addressed only to physicians, not to the general public. Doctors can be expected to understand the prominent statement advising that OxyContin is a Schedule II opioid and to follow a specific direction to 'Please read brief summary of prescribing information including boxed warning on reverse side.' In addition, the new ads will be read by physicians not in isolation as the Warning Letter implies but in light of their education, training, and experience; their familiarity and understanding of Schedule II 	PDD8013024898

		<p>controlled substances required for their DEA licensing to prescribe drugs like OxyContin; their knowledge of OxyContin from the FDA approved labeling for the product (which also appears in the brief summary portion of both advertisements); and their previous exposure to information included in the OxyContin boxed warning.”</p> <ul style="list-style-type: none"> • Purdue ceased to disseminate the two ads in question and plan proposed to run new advertisements featuring the boxed warning as the principal message. <p>Detailed Response</p> <p><i>“Purdue’s Advertisements Include all Pertinent Risk Information in the Brief Summary Portion of the Ads and Properly Repeat or Reference that Risk Information in the Body of the Ads”</i></p> <ul style="list-style-type: none"> • “It is permissible to incorporate risk information into a journal advertisement by use of a cross-reference in the “body” of the ad to a boxed warning appearing in the brief summary portion of the ad” • “...FDA’s regulations permit incorporation of risk information into a journal advertisement by use of a concise cross-reference in the “body” of an ad to a boxed warning appearing the brief summary portion of the ad. DDMAC guidance and an untitled letter, as well as DDMAC’s failure to object to similar competitive ads, all confirm that this approach may be acceptable. • “Purdue’s ads comply with FDA regulations and DDMAC interpretations by providing textual information pertaining to side effects and risks and by prominently directing the reader to the boxed warning information in the brief summary portion of the ad.” • “FDA regulations expressly permit disclosure of information through use of a concise statement referring to a more detailed discussion in another part of the advertisement, and prior DDMAC interpretations confirm specifically that a cross-reference to a boxed warning quoted in full elsewhere in a promotional piece is inadequate. There is simply no basis to conclude that the ‘body’ of Purdue’s ads – which contains both a ‘concise’ statement referring to more detailed information in the brief summary, and additional information taken directly from the boxed warning – is deficient.” <p><i>“The ads do not misrepresent the safety profile of OxyContin by linking the risk of respiratory depression with all opioids.”</i></p> <ul style="list-style-type: none"> • “DDMAC claims that the statement, ‘The most serious risk with opioids including OxyContin, is respiratory depression’ implies that there are no specific safety considerations for OxyContin related to respiratory depression...Purdue questions the basis for DDMAC’s belief that the word ‘including’ in the quoted sentence would be interpreted by physicians to mean ‘excluding.’ 	
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		<p>The sentence clearly and unambiguously conveys that the most serious risk associated with OxyContin is respiratory depression.”</p> <ul style="list-style-type: none"> • DDMAC suggested use of the statement, “the most serious risk with opioids, including OxyContin, is respiratory depression” in a letter from December 20, 1995. <p><i>“The ads do not misrepresent the side effects of OxyContin by linking them to opioids generally.”</i></p> <ul style="list-style-type: none"> • “DDMAC also asserts that describing the side effects listed in the ads as ‘common opioid side effects’ is improper because the listed side effects have been seen with OxyContin itself and should be described as such...The fact that these side effects are associated with opioids generally does not minimize or obscure the fact that these are serious side effects or suggest that they have not been observed with OxyContin itself.” • The concept of referring to “common opioid side effects” was accepted by DDMAC in a letter from December 20, 1995. <p><i>“The ads do not provide incomplete information on contraindications”</i></p> <ul style="list-style-type: none"> • The warning letter asserts that the claim that “OxyContin is contraindicated in ‘any situation where opioids are contraindicated’ is insufficient and the referenced ‘situations’ should be identified with specificity. In fact, this statement is a quote from the <i>Contraindications</i> section of the approved package insert, and the brief summary portion of the ads identifies with specificity the referenced ‘situations where opioids are contraindicated.’” <p><i>“The ads prominently include appropriate information on indications”</i></p> <ul style="list-style-type: none"> • “DDMAC contends that the statement – ‘For moderate to severe pain when a continuous around-the-clock analgesic is needed for an extended period of time’ – is not sufficiently prominent in the body of the ads...These indication statements are presented in clear, bold type, in sharp contrast to the background...In sum, both of these indication statements are prominent and are neither buried, obscured, nor minimized.” <p><i>“The gentleman portrayed in the November ad does not misrepresent the approved indications.”</i></p> <ul style="list-style-type: none"> • “..the fishing man in the November ad is not inconsistent with a typical patient taking OxyContin. The approved package insert instructs physicians to adjust dose to achieve ‘generally mild or no pain.’ If this done, an 	
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		<p>OxyContin patient could engage in a non-strenuous activity such as fishing...”</p> <p><i>“The ads convey that OxyContin is not for PRN use and the visuals in the ads do not convey that OxyContin is appropriate for all hospitalized patients in pain.”</i></p> <ul style="list-style-type: none"> • “Because the recent OxyContin ads include prominent statements of the indication for the drug and no feature of the ads, alone or in context, suggest that the drug can or should be used as a prn analgesic, Purdue does not believe a separate affirmative statement in these ads to the effect that OxyContin is not intended for use as a prn analgesic is warranted or necessary.” <p><i>“The ads will not negatively impact public health”</i></p> <p>“The January 17, 2003 Warning Letter speculates that the two new ads may lead to inappropriate prescribing of OxyContin to the detriment of the public health. This unsupported allegation is unfounded. DDMAC has not presented any evidence (e.g., a copy test of the ads) suggesting that the ads will actually be interpreted in the strained manner discussed in the Warning Letter.”</p>	
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Promotional Material Review & DDMAC Discussions

PURDUE				
Product	Date	To/From FDA	Contents	BATES
OxyContin	10/12/1995	To FDA	Submission of proposed launch materials for review (OxyContin Launch Visual Aid, OxyContin Journal Ad) The materials are based on clinical study data and version #18 of the draft labeling.	PURCHI-000622714
OxyContin	11/30/1995	To FDA	Contents Not Reported	Bates Unavailable
OxyContin	12/1/1995	Call with FDA	Contents Not Reported	Bates Unavailable
OxyContin	12/1/1995	From FDA	Contents Not Reported	Bates Unavailable
OxyContin	12/19/1995	To FDA	<p>DDMAC previously requested “1) verification that the assessment tool used to support this statement has been previously validated, and 2) details concerning how the questionnaire was administered and the detailed results (including statistical testing).”</p> <p>“The Brief Pain Inventory (BPI) has been extensively utilize in cancer and now in non-cancer chronic pain to assess various aspects of pain and how pain interferes with various components of the patients emotional and functional well-being.”</p> <p>“...these results clearly show that treatment with OxyContin did significantly reduce the interference of pain on mood and sleep. Additionally, there is a strong trend toward a reduction in the interference of pain on enjoyment of life and walking ability.”</p>	PURCHI-000621753
OxyContin	12/20/1995	From FDA	<p>DDMAC response to 10/12/95 and 11/30/95 submissions. DDMAC makes several suggestions for changes to misleading statements including, but not limited to:</p> <ul style="list-style-type: none"> “Prompt onset of relief – analgesic action within 1 hour in most patients” FDA response: statement would be misleading because onset of action within 1 hour is not considered prompt relief. “Single-entity agent – contains no aspirin or acetaminophen which may be potentially toxic in high daily dose” FDA response: statement would be misleading because “high 	PURCHI-000622957

			<p>daily dose” is ambiguous and overstates the toxicity.</p> <ul style="list-style-type: none"> • “OxyContin Tablets are to be taken whole. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of potentially toxic dose of oxycodone. The most serious risk associated with opioids is overdose causing respiratory depression...” – FDA response: the balancing information should be enlarged because it isn’t presented with a prominence comparable to the info about drug effectiveness. The sentence “the most serious risk...” would be misleading because it implies that respiratory depression only occurs with overdose. • “The logical next step for patients no longer responding to or tolerating nonopioids: Add to or replace nonopioid with OxyContin. Q12 OxyContin – ideal for initial opioid therapy.” FDA response: statements would be misleading because they imply that patients not responding to nonopioids should move directly to round-the-clock opiates as the next step. OxyContin shouldn’t be presented as step 2 therapy (mild to moderate pain) on the analgesic pain ladder, because round-the-clock opioids are step 3 therapy (moderate to severe pain). • “Percent of patients experiencing onset of pain relief 90%.” FDA response: statement would be misleading because, by referencing this one single-dose study in post-operative patients, it implies that OxyContin is indicated for this patient population. 	
OxyContin	1/10/1996	To FDA	Contents Not Reported	PKY180658462
OxyContin	1/11/1996	To FDA	Purdue’s response to DDMAC’s letter from 12/20/1995 with the company’s responses to DDMAC’s comments.	PURCHI-000622986
OxyContin	1/30/1996	From FDA	FDA’s response to 12/19/1995 submission of a Brief Pain Inventory questionnaire as support for quality of life claims (sleep, get along with other people, enjoy life, perform normal work, walk) in OxyContin	PURCHI-000623095

			<p>promotional materials.</p> <p>FDA's response: Questionnaire doesn't support the above QoL claims. The claims assert that OxyContin doesn't impair functioning, but the questionnaire asked whether pain impairs functioning. This claim doesn't reflect the question asked and would be considered misleading.</p>	
OxyContin	1/31/1996	From FDA	<p>Response from the FDA to Purdue's 1/11/1996 request for comments on revised launch materials.</p> <ul style="list-style-type: none"> • Fair balance statement. FDA Response – balancing statement isn't presented with prominence and readability comparable to the claims made. • “The logical next step for patients, with persistent pain, no longer responding to or tolerating nonopioids.” FDA Response – OxyContin shouldn't be presented as step 2 therapy on the analgesic pain ladder. • “Presentations that include the osteoarthritis trial” FDA Response – it would be misleading to imply that OxyContin is indicated for pain that is not moderate-to-severe. • “In this study, OxyContin 20 mg q 12...significantly decreased pain, improved quality of life, mood and sleep.” FDA Response – claim would be misleading because it fails to disclose that these improvements were in comparison to placebo only. 	PURCHI-000623100
OxyContin	2/4/1996	To FDA	Contents Not Reported	Bates Unavailable
OxyContin	2/6/1996	Call with FDA	<p>FDA had one comment on the 2/4/2003 submission. In the “Dear Healthcare Practitioner” letter PPLP proposed the sentence “[t]his information concerns the abuse liability and potentially fatal risks of respiratory depression associated with the use, and in particular misuse and abuse of OxyContin.” FDA insisted the stick with their suggested text.</p> <p>PPLP informed the FDA that after they took down their company websites on 1/31/2003, they brought the corporate website back up without the News and Announcement section.</p>	PDD8003222805

			<p>“Also I told him that we had ceased dissemination of all of our OxyContin branded promotional materials and would like to submit our revised campaign for their review next week because the only branded piece our sales representatives were using was the package insert.”</p>	
OxyContin	2/6/1996	To FDA	<p>During the 2/5/1996 phone call PPLP requested permission to use 15,000 copies of a visual aid. During the call DDMAC granted approval. The revisions requested in the 1/21/1996 DDMAC letter will be applied in the next printing.</p>	PURCHI-000623103
OxyContin	2/9/1996	To FDA	<p>Purdue submitted revised copies of the launch materials previously reviewed by the FDA (see letters 10/12/1995, 11/30/1995, 12/20/1995, 1/11/1996, 1/30/1996, and 1/31/1996)</p> <ul style="list-style-type: none"> Purdue disagreed with the FDA with regards to the statement “the logical next step for patients, with persistent pain, no longer responding to or tolerating nonopioids.” Purdue disagreed with the FDA’s classifications of Step 2 and Step 3 analgesics. “OxyContin tablets can and should be used in appropriate patients when they develop moderate pain (persistent or increasing) not fully responding to a non-opioid. We, and independent authorities agree, that this is the intention, we feel, of Step 2.” They changed the language to make it clear that OxyContin is indicated for pain of at least moderate intensity. Purdue acknowledged all other suggestions and made the recommended changes. 	PURCHI-000623112
OxyContin	2/27/1996	From FDA	<p>From FDA to Purdue’s letter date 2/9/1996.</p> <ul style="list-style-type: none"> The letter addresses the disagreement over OxyContin being considered used in Step 2 on the pain ladder. FDA Response – they are not persuaded by Purdue’s argument. The revised presentation is misleading as it implies that opioid-naïve patients should start with around-the-clock opioids. There is no evidence to establish that around-the- 	PURCHI-000623168

			clock opioids are preferable to PRN opioids.	
OxyContin	2/29/1996	Call with FDA	Call with the FDA to discuss the 2/27/1996 letter. <ul style="list-style-type: none"> Dr. Wright recognized that certain patient populations (i.e. cancer) would benefit from around-the-clock opioid therapy without first being treated with PRN opioids. Based on his experience, he believes other populations might benefit from first using PRN opioids. Purdue responded they would review available data, consider a study, and in the interim his recommendations would be included in the initial advertising. 	PURCHI-000623233
OxyContin	3/4/1996	To FDA	Fax to FDA with revised launch materials	Bates Unavailable
OxyContin	3/5/1996	Call with FDA	Call to discuss 3/4/1996 submission of advertising copy revised in accordance with comments received in 2/29/1996 phone call. <ul style="list-style-type: none"> Purdue stated they neither agree or disagreed with Dr. Wright's assessment that there was an increase in adverse experiences in patients initially treated with opioids. FDA still took issue with statements focused on "opioid-naïve patient not tolerating opioids." Recommended Purdue either increase the font size of the qualifying statement on non-cancer patients or add "and/or opioids" after the initial statement. Purdue did not agree with "and/or" and asked for only "or" to be used. FDA agreed. 	PURCHI-000623235
OxyContin	3/8/1996	To FDA	Purdue submitted the revised visual aid previously discussed with the FDA in phone calls on 2/29/1996 and 3/5/1996.	PURCHI-000623186
OxyContin	3/13/1996	From FDA	FDA's response to Purdue's submission on 3/8/1996. The FDA had no objections.	PDD8003007491
OxyContin	3/19/1996	To FDA	Contents Not Reported	PKY180658462
OxyContin	3/28/1996	To FDA	Contents Not Reported	PKY180658462
OxyContin	4/3/1996	To FDA	Contents Not Reported	PKY180658462
OxyContin	4/16/1996	To FDA	PPLP's submission of an 8 page draft visual aid produced by Abbott Laboratories.	PPLPC013000093969
OxyContin	4/22/1996	To FDA	Contents Not Reported	PKY180658462
OxyContin	5/9/1996	From FDA	From FDA to Purdue's request for comments from 4/16/1996. <ul style="list-style-type: none"> "The one to start after PCA...The oral choice for pain management 	PURCHI-000623303

			<p>following PCA and APM infusion therapy.” FDA Response: claim “one to start with” should be linked to “around-the-clock” because OxyContin would not be the oxycodone to start unless around-the-clock therapy is needed.</p> <ul style="list-style-type: none"> “Q12h dosing provides smooth and sustained blood levels.” FDA Response: Qualifier “Concentration values adjusted to a mean total daily OxyContin dose of 73 mg” should be more prominent. The presentation should prominently indicate that this data is from steady-state blood levels. 	
OxyContin	5/23/1996	To FDA	Contents Not Reported	Bates Unavailable
OxyContin	5/24/1996	Call with FDA	<p>Call with FDA to discuss 5/23/1996 revised advertising copy submitted in accordance with 5/9/1996 letter from the FDA.</p> <ul style="list-style-type: none"> DDMAC wants it clear that OxyContin is for chronic use (not acute) and that a closer link to the definition would clarify this indication. 	PURCHI-000623336
OxyContin	6/10/1996	To FDA	Contents Not Reported	PKY180658462
OxyContin	6/11/1996	To FDA	Contents Not Reported	PKY180658462
OxyContin	6/28/1996	To FDA	Contents Not Reported	PKY180658462
OxyContin	7/11/1996	To FDA	Contents Not Reported	PKY180658462
OxyContin	9/18/1996	To FDA	Contents Not Reported	PKY180658462
OxyContin	2/20/1997	To FDA	Contents Not Reported	Bates Unavailable
OxyContin	3/3/1997	To FDA	Contents Not Reported	PKY180658462
OxyContin	3/10/1997	Call with FDA	Call with the FDA to request the review status of the OxyContin 80 mg promotional package submitted on 2/29/1997. PPLP advised that the review was ongoing.	PURCHI-000623385
OxyContin	3/24/1997	From FDA	<p>From FDA on Purdue submission from 2/20/1997 with request for comments on promotional materials for OxyContin 80 mg tablets.</p> <ul style="list-style-type: none"> Journal article – FDA Response: concerned with statement that maximum dose of acetaminophen and aspirin are potentially toxic. This would be misleading. Should more prominently present the precaution that the new 80 mg tablet is for use in opioid tolerant-patients requiring daily oxycodone equivalent dosages of 160 mg or more. MD Announcement Letter – FDA Response: Should disclose 	PURCHI-000623387

			<p>OxyContin isn't recommended pre-operatively or for the management of pain in the immediate post-operative pain for patients not previously taking the drug because its safety hasn't been established in this setting.</p> <ul style="list-style-type: none"> Flashcard – FDA Response: See above re: MD Announcement Letter 	
OxyContin	3/27/1997	Call with FDA	<p>Call to clarify comments from 3/24/1997 FDA letter.</p> <ul style="list-style-type: none"> Discussed the differences in the FDA response on aspirin and acetaminophen from the 12/20/1995 letter on 10, 20, and 40 mg tablets. FDA would review previous letter. Fair balance statement for “not recommended preoperatively” is needed if sent to surgeons 	PURCHI-000623397
OxyContin	4/15/1997	To FDA	Contents Not Reported	Bates Unavailable
OxyContin	4/21/1997	To FDA	<p>Response from Purdue to 3/24/1997 letter and 3/27/1997 phone call to clarify statements in the MD Announcement letter.</p> <ul style="list-style-type: none"> The letter doesn't include post-operative statement as it is not primarily directed to surgeons In any letters which are directed to surgery, the following would be included: “OxyContin is not recommended pre-operatively or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery)” 	PURCHI-000623441
OxyContin	4/21/1997	Call with FDA	<p>Call to confirm receipt of 4/21/1997 response to FDA's letter on 3/24/1997.</p> <ul style="list-style-type: none"> Tentatively agreed that the revised statement “OxyContin is not recommended pre-operatively or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery)” was appropriate. Would send a “final” recommendation on the Journal Ad. 	PURCHI-000623441
OxyContin	4/24/1997	From FDA	<p>FDA's comments on 4/15/1997 revised submission.</p> <ul style="list-style-type: none"> Journal Advertisement – FDA Response: still concerned about statement “Single-entity agent – 	PURCHI-000630870

			contains no aspirin or acetaminophen which have added potential toxicities when exceeding recommended daily doses.” Drugs are not always toxic when the maximum doses are exceeded and this suggest that there is no toxicity associated with use of OyxContin, which is inconsistent with the PI.	
OxyContin	4/28/1997	To FDA	Response to FDA comments from 4/24/1997. <ul style="list-style-type: none"> Statement “Single-entity agent – contains no aspirin or acetaminophen which have added potential toxicities when exceeding recommended daily doses” has been changed to “Single-entity agent – contains no acetaminophen or aspirin. Unlike Percocet, Vicodin, Lorcet, or Tylenol with codeine, OxyContin may be doses as high as clinically necessary.” 	PURCHI-000630870
OxyContin	4/29/1997	Call with FDA	Call to confirm receipt of 4/28/1997 revised promotional material. New statement was approved.	PURCHI-000623463
OxyContin	5/9/1997	To FDA	Contents Not Reported	PKY180658462
OxyContin	5/19/1997	Call with FDA	Call to follow up on 4/29/1997 call wherein preliminary verbal approval was given to statement “single-entity contains no acetaminophen or aspirin...” Received final confirmation and approval for use of the statement.	PURCHI-000630945
OxyContin	9/10/1997	To FDA	Contents Not Reported	PKY180658462
OxyContin	9/23/1997	To FDA	Contents Not Reported	PKY180658462
OxyContin	3/3/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	3/11/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	4/9/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	4/28/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	5/13/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	5/26/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	6/15/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	7/6/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	8/28/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	9/15/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	10/12/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	11/20/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	12/8/1998	To FDA	Submission of OxyContin Slim Jim, CCP Pain Management Inservice Module, OxyFAST Flashcard, and OxyContin/OxyIR/OxyFAST artwork for review	PURCHI-000817736

OxyContin	12/9/1998	To FDA	Contents Not Reported	PKY180658462
OxyContin	1/22/1999	To FDA	Contents Not Reported	PKY180658462
OxyContin	2/23/1999	To FDA	Contents Not Reported	PKY180658462
OxyContin	3/16/1999	To FDA	Contents Not Reported	PKY180658462
OxyContin	4/20/1999	To FDA	Submission of OxyContin promotional materials including, Precise Letter: Low Back Pain artwork, Precise Letter: Post-Op Pain artwork, Precise Letter: Postherpetic Pain, Precise Letter: Osteoarthritis, "Stand Alone" Side Effects brochure, Literature Reprint: "The Role of Opioids in Treatment of Arthritis," Good Samaritan Reference Cards, and Price List from Red Book	PURCHI-000816988
OxyContin MS Contin	5/11/1999	To FDA	Submission of OxyContin Price list, MS Contin price list, and New 4 th Edition of American Pain Society Booklet: Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain for review	PDD8023035114
OxyContin	6/2/1999	To FDA	Submission of the following OxyContin promotional materials: Low Back Pain reprint carrier, Osteoarthritis reprint carrier, Patient Profiles Visual Aid, Managed Care Long-Term Care Case Study: Rehabilitation Patient, Managed Care Long-Term Care Competition Visual Aid, Post-Op Patient Profiles Case Study Flashcard, Post-Herpetic Neuralgia Case Study, 18-Month Calendar, Core Competition Visual Aid, OxyContin [ABC] vs. Morphine Flashcard, Price list	PURCHI-000550254
OxyContin	6/23/1999	To FDA	Submission of the following OxyContin promotional materials for review: Direct Mail Campaign: Wave 1 – Keep it Simple, Revised Fast Onset Flashcard, New OxyContin vs. Roxycodone SR Visual Aid, Revised Long Term Care Handbook (Managed Care), 1999 Pain Management Prescribing Guide, Price list	PURCHI-000550536
OxyContin	7/16/1999	To FDA	Submission of OxyContin Patient to Patient Video in Spanish, "Clock" Premium Giveaway, and Price list for review	PKY180800452
OxyContin	8/27/1999	To FDA	Submission of OxyContin promotional materials, Addiction Terminology Flash Card, Fast Onset Flash Card, and Price list for review	PKY181120466
OxyContin	10/4/1999	To FDA	Submission of the following OxyContin promotional materials for review: Reprint: "Management of Chronic Non-Cancer Pain: A Guide to Appropriate Use of Opioids" by Jennifer Schneider, MD, Revised Managed Care Long-Term Care Rehabilitation Case Study, Product Data Brochure, and price list	PKY180800333

OxyContin	10/12/1999	To FDA	PPLP submitted a draft eight-page visual aid produced by Abbott Laboratories for review. The piece incorporates revisions made to the recently approved visual aid.	PKY180643221
OxyContin	10/14/1999	To FDA	PPLP references submission on 3/8/1996 request for comments on revised visual aid and the 3/13/1996 response from DDMAC approving its use. PPLP submits a draft 8 page visual aid produced by Abbott Laboratories for review.	PKY181053824
OxyContin	10/15/1999	To FDA	PPLP submitted a revised visual aid.	PKY81053808
OxyContin	1/25/2000	To FDA	Submission of the following OxyContin promotional materials for review: Revised OxyFast Flashcard, NHC OxyContin Binder Page, New OxyContin Reprint: Treatment of Osteoarthritis Pain with Controlled Release Oxycodone...(Caldwell), MHC OxyContin Fact Sheet, New OxyContin Dr. Spanos Patient Follow-up Video	PDD1501608036
OxyContin	3/9/2000	To FDA	Submission of the following OxyContin promotional materials for review: Revised Post-Op Pain Flashcard, Revised OxyContin/OxyIR/OxyFast Slim Jim, Revised OxyContin "No Ceiling" Visual Aid, Price list	PDD8013000780
OxyContin	3/10/2000	To FDA	Submission of Myths About Opioids for review	PDD8013000821
OxyContin	4/6/2000	To FDA	Submission of the following OxyContin promotional materials for review: Oxy vs. combo visual aid, OxyContin patient information booklet, New OxyContin reprint, Revised OxyContin side effects management guide, OxyContin new managed care demographic visual aid	PURCHI-000624352
OxyContin	4/20/2000	To FDA	Initial launch package for 160 mg tablets containing a flashcard, press release, and "Dear Health Care Provider" letters.	Bates Unavailable
OxyContin	5/8/2000	Call with FDA	Call to obtain status of the review of the launch package for 160 mg tablets.	PURCHI-000817046
OxyContin	5/10/2000	To FDA	Submission of the following OxyContin promotional materials for review: OxyContin ONS Convention Quiz Pad, OxyContin 160 mg "No Claims" Sell Sheet, OxyContin Scroll Pen, OxyContin "Daytimer" Inserts: Conversion, Titration, Assessment, "I Got My Life Back" Part II CD Rom, OxyContin/Managed Care PCS Preferred Drug Listing Sheet, OxyContin 160 mg GPO Sell Sheet [Medicaid], price list	PDD1501608529
OxyContin	5/15/2000	From FDA	Response to Purdue's 4/20/2000 submission for 160 mg tablet launch materials.	PURCHI-000630857

			<p><i>Flashcard</i></p> <ul style="list-style-type: none"> • FDA Response: Suggestion that OxyContin 160 mg can be used as initial opioid therapy is inconsistent with the PI and thus misleading. • Selectively present information regarding the bolded precaution for OxyContin 160 mg. Presentation fails to present that OxyContin 160 mg is comparable to two 80 mg tablets when taken on an empty stomach and that dietary caution should be taken when patients are initially titrated to 160 mg. • Promotes OxyFast which is in violation of section 201(p) of the Federal Food, Drug, and Cosmetic Act as it promotes an unapproved new drug. • “Prompt onset” is misleading because onset of action within 1 hour is not considered prompt relief. • Object to the lack of fair balance with respect to content and presentation of risk information. • Dosing presentation is misleading because it presents information concerning the initiation of OxyContin without also presenting important risk information regarding cessation. <p><i>Press Release</i></p> <ul style="list-style-type: none"> • FDA Response: “For patients suffering from moderate to severe pain which requires treatment for more than a few days, such as pain associated with arthritis, cancer, injuries, lower back problems, and other musculoskeletal conditions...” Statement is misleading because it suggests that OxyContin 160 mg can be used as first line therapy for the treatment of the above conditions and lacks important qualifying contextual information stated in the PI. • Claim of improved quality of life in 700 patients is misleading because it suggests the results of the study in osteoarthritis patients are more 	
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			<p>representative than they actually are.</p> <p><i>Dear Health Care Provider Letters</i></p> <ul style="list-style-type: none"> “Oxycontin has always been the opioid to start with and stay with as initial therapy in steps 2 and 3 of the World Health Organization’s analgesic stepladder.” FDA Response: OxyContin is just one of the many opioids that can be used and thus this statement is misleading. This claim lacks important contextual information concerning other types of pain medications, such as prn opioids or combination products that may also be appropriate in pain management. 	
OxyContin	5/26/2000	To FDA	Purdue’s response to the FDA letter from 5/15/2000 on the 160 mg launch materials. Purdue complied with all of DDMAC’s recommendations.	PURCHI-000630685
OxyContin	6/9/2000	To FDA	Submission of the following OxyContin promotional materials for review: Literature Reprint: “Around-the-Clock, Controlled-Release Oxycodone Therapy for Osteoarthritis-Related Pain,” Physician Authorization Form, Diskette containing OxyContin Physician Authorization Form, Managed Care Patient Demographics Reference Visual Aid-Overhead Acetates, Managed Care Sell Sheet for OxyContin 160 mg Tablet, Price list	PDD8013001778
OxyContin	6/15/2000	From FDA	<p>FDA’s response to Purdue’s submission of revised promotional materials from 5/26/2000.</p> <ul style="list-style-type: none"> The Dear Health Care Letter suggests OxyContin 160 mg can be used in initial opioid therapy. Reiterate that the bolded precaution that states OxyContin 160 mg is for use only in opioid tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more, be presented before, or in conjunction with, the claims that introduce this new strength to OxyContin. 	PURCHI-000662598
OxyContin	6/28/2000	From FDA	FDA’s response to PPLP’s 5/25/2000 response to the Warning Letter. The FDA reviewed their response and found the actions taken acceptable.	PKY180545319
OxyContin	6/28/2000	To FDA	Submission of OxyContin 2000 PCS	PDD8013002228

			Performance Drug List Sheet, OxyContin/OxyIR/OxyFast Calendar, and price list	
OxyContin	8/25/2000	To FDA	Submission of Revised OxyContin Flashcard and Patient Starter Program #4 for review	PDD8013002618
OxyContin	9/8/2000	To FDA	Submission of the following OxyContin promotional materials for review: AHCPR Post-Operation Pain Patient Guide [Spanish], New Complete Pain Management: An Overview Slide Kit #2, 160 mg tablet Hospital Pharmacist Introduction Letter and Envelope, 160 mg tablet Nurse Introduction Letter and Envelope, Envelope directed to Hospice Nurse, Envelope directed to Oncology Nurse, Envelope directed to Pain Clinic Nurse	PDD8013002661
OxyContin	9/14/2000	To FDA	Submission of Myths About Opioids promotional item for review	PDD8013002926
OxyContin	10/2/2000	To FDA	Submission of OxyContin 160 mg File Card and Photo Visual Aid for review	PDD8013002964
OxyContin	10/18/2000	To FDA	Submission of the following OxyContin promotional materials for review: OxyContin/OxyIR Slim Jim, Long Term Care Case Study, Addiction Terminology Flash Card, Post Herpetic Neuralgia Flash Card, Literature Reprint: "Conversion from IV PCA Morphine to Oral Controlled-Release Oxycodone Tablets [OxyContin] for Postoperative Pain Management"	PDD8013003082
OxyContin	10/30/2000	To FDA	Submission of OxyContin Long Term Care Case Study: (Musculoskeletal) and Titration Wall Chart for review	PDD8013003124
OxyContin	11/17/2000	To FDA	Submission of the following OxyContin promotional materials for review: File Card, Telephone Message Pad, PCA Conversion Wall Chart, OxyContin vs. Short Acting Visual Aid, Reprint Carrier re: Low Back Pain, 160 mg Flash Card, Patient Profile Visual Aid, Extended OxyContin Patient Starter Program	PDD8013003177
OxyContin	11/30/2000	To FDA	Submission of CD Rom Medical Liaison Slide Presentation entitled "Description of Food-Effect When Administering OxyContin (oxycodone HCl controlled-release) Tablets C-11; 160 mg Tablets	PDD8013003278
OxyContin	1/24/2001	From FDA	Letter from DDMAC advising that they have become aware that some narcotics pain medications are being promoted for the management of breakthrough cancer pain. "Currently Actiq...is the only narcotic pain medication specifically indicated for the	PDD1782000706

			management of breakthrough cancer pain. The Agency is unaware of substantial evidence that supports the use of other narcotic pain medications for the management of this specific type of pain. Therefore, any promotional materials or activities that state or suggest that narcotic medications, other than Actiq, are useful for the management of breakthrough cancer pain are misleading because they promote an unapproved new use.”	
OxyContin	1/24/2001	To FDA	Submission of the following OxyContin promotional materials for review: Quest Letter – Onset of Action, Quest Letter – “Start With/Stay With”, Quest Letter – Thank You For Seeing Me, Quest Letter – Easy to Dose, Quest Letter – Post-Therapeutic Neuralgia, Long-Term Care Reprint & Carrier, “Partners Against Pain” Pain Assessment Scale, Q12h Flash Card, Long-Term Care Handbook, “Partners Against Pain” 0-10 Pain Scale	PDD8013003649
OxyContin	1/30/2001	Call with FDA	Call to discuss planned 3/27/01 meeting with FDA. DDMAC has concerns that certain products labeling currently contained recommendations regarding usage for breakthrough cancer pain. Purdue said they would submit a formal response.	PURCHI-000672977
OxyContin	1/31/2001	To FDA	Letter to the FA re: 3/27/01 meeting. <ul style="list-style-type: none"> “We are surprised that you indicate that the promotion of oxycodone for breakthrough cancer pain is in violation of the Federal Food, Drug, and Cosmetic Act.” 	PURCHI-000672972
OxyContin	2/6/2001	To FDA	Submission of the following OxyContin promotional materials for review: Quest Letter – To Live With, Quest Letter – Osteoarthritis Followup, Quest Letter – versus PCA, Reprint Carrier – Watson, Fast Onset Flash Card, Long-Term Care Competition Visual Aid, Daytimer Insert, Case Study Video: “I Got My Life Back” Dr. Spanos, Patient in Pain Video, Case Study Video: “I Got My Life Back – Part II” Dr. Spanos.	PDD8013070058
OxyContin	2/20/2001	To FDA	Submission of the following OxyContin promotional materials for review: Quest Letter – Intermittent vs. Persistent Pain, Quest Letter – Low Back Pain, Quest Letter – Post Op, Quest Letter – OxyIR for breakthrough, Quest Letter – Neuropathic	PDD8013004276

			Pain, OxyContin "Delivers" Flash Card, Dosing Guide, Visual Aid	
OxyContin	3/9/2001	Call with FDA	Voice mail re: 3/27/01 meeting. FDA said there was no agenda for the meeting but would discuss the issues outlined the agency letter.	Bates Unavailable
OxyContin	3/16/2001	Call with FDA	<p>FDA requested teleconference with Purdue on their "current opinions and actions in relation to drug abuse and diversion with OxyContin."</p> <ul style="list-style-type: none"> FDA is concerned on status of diversion and drug abuse of OxyContin. The planned meeting on 4/23/01 is too far away and the FDA wants Purdue's perspective. Purdue's approach to the issue will be "developing partnerships with regulatory, law enforcement, community groups and government agencies. Educational programs have been developed and a number of abuse and diversion actions are being developed." FDA responded that this is a legitimate national health problem. Agency is committed to "find out the extent and nature of the abuse, as well as look at the oral versus intravenous versus intranasal use." FDA requested more information on Purdue's educational efforts. FDA further asked about Purdue's efforts in targeting kids. FDA responded that "both the Agency and PPLP are under scrutiny as the publicity is increasing and therefore she would appreciate receiving a copy of the brochures and other materials." FDA asked what Purdue is doing re: consideration of reformulation. Purdue responded, "research seems to show that the abuse is more common with the IV dosage form over the oral which supports PPLP's current effort to develop an oxycodone and naloxone combination due to naloxone's low oral bioavailability." FDA wanted to discuss the intranasal bioavailability data. 	PURCHI-000674146

			<ul style="list-style-type: none"> FDA stated “that in a recent discussion with law enforcement, she was informed that oxycodone is getting to be as abused as hydrocodone and the company should be aware of that as it proceeds...PPLP should re-examine our protocols...in an hydrocodone protocol, a 30-day supply of OxyContin is being given at the end of the trial.” FDA asked if Purdue had any ideas to address the problem in the short term. Purdue responded they are using their sales force to educate physicians and pharmacists against drug scams, doctor shopping etc. and their efforts have been effective. FDA cautioned Purdue not to minimize the situation, as “it has the potential to put pain management back in the dark ages.” 	
OxyContin MS Contin	3/19/2001	To FDA	<p>Purdue’s response to the FDA’s letter from 1/24/01 on the promoted management of breakthrough cancer pain.</p> <ul style="list-style-type: none"> Purdue disagrees with the agency’ position that “(1) breakthrough cancer pain is a ‘specific type of pain’ justifying a separate indication and (2) promotion of an opioid medication for breakthrough pain, other than Actiq, should be considered misleading and/or an unapproved new use.” <p>Purdue believes there is scientific, clinical and regulatory support that “breakthrough pain” is within OxyContin & MS Contin’s approved label</p> <ul style="list-style-type: none"> Purdue believes “breakthrough pain is not a separate and distinct type of pain that differs physiologically from pain associated with the underlying condition being treated. It does not warrant a separate indication but does require information on how such pain can be moderated.” 	PURCHI-000674126
OxyContin	3/19/2001	Call with FDA	Discussion on the list of attendees for the 3/27/01 meeting	PURCHI-000674152
OxyContin	3/20/2001	To FDA	PPLP provides list of attendees for 3/27/2001 meeting	PKY180800878

OxyContin	3/27/2001	Meeting FDA	<p>Breakthrough Pain Meeting</p> <ul style="list-style-type: none"> • FDA believes there are two issues to discuss: (1) is breakthrough pain a separate indication and (2) the mention of breakthrough pain in products' labeling. • Purdue responded that they do not believe breakthrough pain is a separate indication but rather it is a "concept which evolved after the introduction of controlled release opioids for the treatment of pain. Breakthrough pain is an educational tool which is used to help physicians titrate dosages of long acting formulations and to manage exacerbations of the underlying pain, not a separate kind of pain." • Dr. McCormick (FDA) responded that what Purdue described is the standard of medical practice. She described breakthrough pain as a distinct entity. She said the Agency learned a lot from Actiq on the nature of breakthrough pain. • Purdue reiterated their position that breakthrough pain is a concept. "He also mentioned that Actiq is only approved for a limited indication for reasons of safety, not because it is the only therapy that works." • FDA conceded that breakthrough pain is specific to the patient but isn't necessarily to an anatomical origin. Also, there was no data besides the Actiq data concerning appropriate dosing, onset of action, and duration of effect. This data would be needed for the company to promote for breakthrough pain. • FDA has no objection to the use of the term breakthrough pain but they need specific information for a formulation or you may be treating the wrong condition with the wrong drug. Indicated the studies could be small studies as opposed to large, Phase III type trials. • Purdue responded that there is a lot of literature to support the appropriate dosing of short term 	PURCHI-000674498
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			<p>opioids and that pharmaceutical companies don't recommend long acting medications for breakthrough pain, only the 4-6 hour drugs. "To have one drug be the only one labeled to treat breakthrough pain means that physicians would have to engage in off-label use of controlled substances and this would make physicians very uncomfortable to prescribe these types of products."</p> <ul style="list-style-type: none"> • FDA said that the standard of practice and what goes in the label are different. • FDA ended the meeting by "declaring that this was a promotional issue and the Agency needs data to support the indication if a sponsor wishes to promote this separate indication. He stated that the other sponsors (who had not attended this meeting) had already agreed to cease promotion of this indication. Purdue needed to inform DDMAC no later than 4/30/01 if they intended to continue to promote this unapproved new claim." 	
OxyContin	4/4/2001	To FDA	<p>Submission of the following OxyContin promotional items for review: Partners Against Pain Winter 2001 Newsletter on CD, Hospital Panel, Post-Operative File Card, Scroll Pen, PCS Performance Drug List, "Taking Control of Your Pain" Booklet, Quest Letter – Connecticut AIDS Drug Assistance Program Formulary, Titration Guideline Card, Slim Jim, Case Study Booklet: "I Got My Life Back, Part II," Visual Aid: Pain Management Internet Guide</p>	PDD8013004694
OxyContin	4/6/2001	To FDA	<p>Follow up letter from Purdue on the "breakthrough pain" meeting held on 3/27/01.</p> <p>"It is our understanding from this meeting that we are required to notify DDMAC of our decision regarding the recommendation for dosing of immediate release opioids for 'breakthrough pain' in our advertising and promotional materials. We agree to comply with your request to cease the promotion of specific dosing recommendations for</p>	PPLPC009000037297

			immediate release opioids analgesics for treating 'breakthrough pain' in our promotional materials as soon as it is practicably feasible."	
OxyContin	4/16/2001	To FDA	<p>Revised follow-up letter from Purdue on the "breakthrough pain" meeting. Same language as the 4/6/2001 letter expect for the addition of the following:</p> <ul style="list-style-type: none"> Purdue states it will take 10 weeks after receipt of approved new promotional pieces to replace the previous pieces. It will take a total of approximately 12 weeks. "We ask that we be allowed to continue to use the current materials until that time so that we can utilize them for the remaining appropriate promotional messages that are also contained in these pieces." 	PPLPC009000037671
OxyContin	4/19/2001	To FDA	Purdue agrees to comply with DDMAC's request to cease the promotion of specific dosing recommendations for immediate release opioid analgesics for treating "breakthrough pain." Purdue estimated it would take approximately 12 weeks to get revised promotional materials to their sales representatives. Purdue asked to be allowed to continue to use the promotional materials "so that we can utilize them for the remaining appropriate messages that are also contained in these pieces."	PURCHI-000674491
OxyContin	5/1/2001	To FDA	Submission of the following OxyContin promotional items for review: Managed Care: Revised Rehab Patient Long-Term Care Case Study, Managed Care: Revised Long-Term Care Case Study – Musculoskeletal Pain, Binder Page for Managed Care White Paper, Press Release dated 3/28/2002 entitled "Prescription Protection Program Offered to <i>Arkansas</i> Physicians," and Press Release dated 3/28/2002 entitled "Prescription Protection Program Offered to <i>Louisiana</i> Physicians,"	PURCHI-000696517
OxyContin	6/8/2001	To FDA	Submission of 2001 Pain Management Prescribing Guide for review	PDD8013006196
OxyContin	6/14/2001	Meeting with FDA	<p>Meeting with Purdue & FDA (DDMAC, Anesthetic, Critical Care and Addiction Drug Products, Controlled Substances Staff)</p> <ul style="list-style-type: none"> FDA had concerns with the clinical trial section of the package insert. DDMAC "believes that much of 	<p>PURCHI-000679232</p> <p>PURCHI-000723897</p>

			<p>study references should come out of the package insert because these references allow PPLP to promote for implied claims such as ‘osteoarthritis.’”</p> <ul style="list-style-type: none"> • The main issue was the description of the patients in the dose trial as “osteoarthritis” patients. It was left that Purdue would work out this issue with future drafts of the PI and mock-ups of revised promotional materials would be sent to DDMAC. 	
OxyContin	6/18/2001	To FDA	Purdue submits a new draft package insert following the meeting with the FDA on 6/14/01. Advise that they are preparing mock-ups of their revised promotional materials for DDMAC review.	PURCHI-000678532
OxyContin	6/20/2001	To FDA	Submission of the following OxyContin promotional items for review: Slides for State Medical Society Briefings: “A Movement at Risk – Pain Patients and Physicians Under Attack,” Lecture Speakers’ Bureau Letter – Anti-Diversion, Presentation Instructions for the Representatives – Instruction Sheet, Complete Pain Management: Malignant Pain Management Slide Kit, Complete Pain Management Self Assessment: Non-Malignant Pain, Complete Pain Management Self Assessment: Malignant Pain, Spanish Patient Information Booklet, “Stand-By” Anti-Diversion Statement, ONS Convention Quiz Pad	PDD8013006909
OxyContin	6/22/2001	To FDA	Purdue submits draft copies of three representative promotional pieces as color flats, which incorporate recommendations made at the 6/14/01 meeting.	PURCHI-000678787
OxyContin	6/24/2001	From FDA	FDA advises that they have become aware that some narcotic pain medications are being promoted for the management of breakthrough cancer pain. Actiq is the only narcotic pain medication indicated for the management of breakthrough cancer pain. “The Agency is unaware of substantial evidence that supports the use of other narcotic pain medications for the management of this specific type of pain. Therefore, any promotional materials or activities that state or suggest that narcotic medications, other than Actiq, are useful for the management of breakthrough cancer pain are misleading because they promote an	PURCHI-000672928

			unapproved new use.”	
OxyContin	6/27/2001	To FDA	<p>Purdue submits a draft of the “Dear Health Care Professional” letter requested by the FDA. The letter addresses changes to the prescribing information regarding abuse.</p> <p>“Because of reports of illegal misuse, abuse, and diversion of OxyContin Tablets from various parts of the country, Purdue Pharma L.P. has worked with the Food and Drug Administration to revise sections of the prescribing information, specifically 1) the WARNINGS with regard to misuse, abuse and diversion and 2) to more carefully describe the appropriate patient population for whom this product is intended.”</p> <p>“The abuse and diversion of prescription drugs has become a significant public health problem in the United States. For this reason, the FDA has called upon the distributors of all Schedule II and III narcotics to make similar revisions in the prescribing information for their products.”</p>	PURCHI-000678838
OxyContin	6/28/2001	Call with FDA	<p>Call to discuss the proposed package insert, promotional materials, and Dear Doctor Letter.</p> <p>Draft Promotional Materials</p> <p>“It was indicated that the quality-of-life claims that are made ‘will have to come out’...In addition there needs to be some additional fair balance in certain sections (DDMAC is to propose specific items) and, in some places, the indication is shortened to say <i>moderate to severe pain</i>. In these places FDA would like the additional portion of the indication included (<i>i.e. where an around-the-clock analgesic is needed for an extended period of time</i>).”</p> <p>Dear Doctor Letter</p> <p>“FDA doesn’t like the last paragraph and Dr. Jenkins will not allow this letter to be tied to correspondence from FDA. In addition, when we refer to the revised warnings, they need to be called “boxed warnings.”</p>	PURCHI-000678855
OxyContin	7/11/2001	Call with FDA	<p>Call with Dr. McCormick from the FDA on the risk management plan.</p> <p>“...both DDMAC and the Division had</p>	PURCHI-000679669

			problems with our promotional proposal (i.e., the prominence of the abuse and diversion messages, the indication and the message 'Not for PRN use')."	
OxyContin	7/12/2001	To FDA	Submission of OxyContin PCS Patient Starter Program for review	PDD1501610320 at 65
OxyContin	7/16/2001	Meeting with FDA	<p>Discussion with the FDA on labeling, draft promotional materials, risk management plan, and manufacturing activities.</p> <p>Draft Promotional Materials</p> <p>"Mr. Askine indicated it was normal policy for DDMAC to ask that, when significant new labeling was approved, that sponsors cease distribution of all promotional materials within 30 days of the approval of the new labeling. DDMAC is not familiar with the details in the pieces but did have some general comments on the promotional pieces. Dr. McCormick indicated that the promotional materials were one part of the overall efforts and thought to be occurring the following order:</p> <ol style="list-style-type: none"> 1. Dear Healthcare Professional Letter 2. Retrain the sales force 3. Revised promotional materials 4. Outreach Educational Program 5. Seek Partnerships with Societies 6. Reformulation with an antagonist" <p>Revised promotional materials were to be submitted for review within two weeks.</p> <p>"The general comments which were reported included 1) each spread should include a reference to the black box warning and its location, 2) increase the prominence of the risk information, 3) contraindications and warnings should be displayed more prominently, and 4) the full indication (four paragraphs) should appear at least once in the piece."</p>	PURCHI-000679574
OxyContin	7/23/2001	To FDA	PPLP submitted draft mock-ups of a revised detail aid that incorporated changes suggested by Dr. McCormick during the 7/16/2001 meeting and 7/17/2001 call.	PURCHI-000679412
OxyContin	7/30/2001	To FDA	Submission of OxyContin "Dear Doctor" Letter and envelope for review	PDD1501610320 at 117
OxyContin	8/2/2001	Call with FDA	Call with DDMAC to discuss their general concerns with the promotional piece submitted on 7/23/01.	PURCHI-000679592

			<ol style="list-style-type: none"> 1. "Overall, the risk section needs to be revised to be reasonably comparable to the presentation of the efficacy claims (i.e. spacing, bolding, font size and presentation)." 2. "Certain risk concepts that are in the revised package insert are not found in the visual aid (i.e. information from the Misuse, Abuse and Diversion section, the Drug Abuse and Dependence section, the second warning under the 80 mg and 160 mg statement regarding respiratory depression, and the 'Not indicated for pre-emptive analgesia' statement" 3. "The information in the boxed warning needs to be updated and must be displayed more prominently." 4. "The indication needs to be displayed more prominently, and it was suggested that headers be used and to possibly add a safety section." 5. "In the patient profiles, the references to qualify of life must be removed unless we have specific data to support it (i.e. reference to unable to work, qualify of relationships, nighttime awakening etc.)" 6. "(Page 3) The statement 'Convenient q12h schedule – won't interfere with patients' daytime activities or nighttime rest, and encourages compliance' can not be used; only reference to convenience is acceptable." 7. "(Page 7) The graph which presents the 20 mg data must be revised to include placebo and the 10 mg to adequately represent the study that supports this graph." 8. "(Page 9) The bullet point 'quality of sleep' should be deleted because this was not adequately proven in the study. Sally Riddle and Tony Goodman pointed out that this was adequately studied by a validated method, and DDMAC agreed to recheck this with the Anesthetics Division." 	
OxyContin	8/3/2001	From	FDA advises Purdue that DDMAC has	PURCHI-000679596

		FDA	<p>reviewed the revised labeling and that all promotional materials for OxyContin that include representations about OxyContin should be revised to include the new risk information.</p> <p>“These revisions should include prominent disclosure for the important new risk information that appears in the revised PI. For example, the following new information should be prominently disclosed:</p> <ul style="list-style-type: none"> • Information contained in the new boxed warning • New warnings that address OxyContin’s misuse, abuse, diversion, and addiction • New precautions and revised indications” 	
OxyContin	8/7/2001	To FDA	<p>PPLP’s response to the 8/3/2001 FDA letter that stated that their promotional materials that include representations about OxyContin should be revised to include the new risk information. PPLP advises they will comply with the request and will only disseminated promotional materials that have been revised to include this new risk information. PPLP attached revised detail aids for review.</p>	PDD8013090307
OxyContin	8/10/2001	From FDA	<p>FDA responds to Purdue’s request for comments on proposed promotional materials from 8/7/2001.</p> <p>Minimizing Risks</p> <ul style="list-style-type: none"> • “‘24 Hours of Pain Control The Easy Way’ – your implication that OxyContin is the ‘easy way’ minimizes the serious and potentially life-threatening risks associated with OxyContin...” • Claim that ‘Controlled-release oxycodone administered every 12 hours provides effective and well tolerated pain control,’ (emphasis added) also minimizes the risks associated with OxyContin.” FDA recommended deletion of this statement. <p>Overstatement of Efficacy</p> <ul style="list-style-type: none"> • “Plumber pictured in the sales aid does not appear to have persistent, moderate to severe pain. Therefore, 	PURCHI-000679881

we recommend you revise this visual to more adequately portray a person who has persistent, moderate to severe pain.”

Unsubstantiated Claims

- Claim: “OxyContin will improve quality of sleep and other parameters such as general activity, walking ability, normal work, and relations with others. These claims are misleading because improvements in these outcomes have not been demonstrated by substantial evidence.”
- Claim: “‘Manage breakthrough pain, if necessary with immediate-release opioid medications.’ This claim is misleading because it suggests that all immediate-release opioid medications have been proven effective for the management of breakthrough pain when such is not the case.”
- Claim: “‘Management of side effects enhances compliance.’ There are many factors other than side effects that influence patient compliance. Compliance claims require substantial evidence in the form of adequate and well-controlled clinical trials. Therefore, your claim that the management of OxyContin side effects enhances compliance is misleading because such has not been demonstrated by substantial evidence.”
- Claim: “‘Clinically proven efficacy in moderate to severe pain associated with cancer, low back pain, and osteoarthritis.’ This claim is misleading because it suggests that OxyContin has been clinically proven to be effective in the pain of each of these specific disease states when such has not been demonstrated by substantial evidence. Therefore, we recommend you revise this claim to, ‘Appropriate for use in moderate to severe pain when associated with conditions such as cancer, low back

			<p>pain...”</p> <p>Fair Balance</p> <ul style="list-style-type: none"> “Your sales aid fails to present important new warnings from the PI concerning the potential for OxyContin drug abuse and diversion. Specifically, we recommend that you prominently present that, ‘OxyContin, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised,’ and ‘Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help limit abuse of opioids.’ We also recommend prominently presenting the bolded warning from the PI beginning with the statement, ‘This risk is increased with concurrent abuse of alcohol and other substances...’ in conjunction with the risk information on misuse and abuse that is already presented on page 15.” 	
OxyContin	8/15/2001	To FDA	Submission of the Partners Against Pain Website Update for review	PDD8013112548
OxyContin	8/20/2001	To FDA	Submission of American Geriatrics Society Quick Reference: “The Management of Chronic Pain in Older Persons”	PDD8013008367
OxyContin	9/17/2001	To FDA	Submission of Briefing Document entitled “OxyContin Tablets: Proper Use vs. Criminal Abuse” and Package Insert Slide Kit for Medical Liaisons – CD-ROM	PDD1501610320 at 166
OxyContin	10/11/2001	To FDA	<p>Purdue responds to DDMAC’s comments from the 8/10/01 letter.</p> <p>Minimizing the Risk</p> <ul style="list-style-type: none"> The phrase “The Easy Way” was replaced with “The OxyContin Way.” “In our opinion, the identical claim and graphic presentation in the new detail aid does not minimize the risks associated with OxyContin therapy.” Purdue does not agree with the FDA’s comment on the phrase, 	PURCHI-000682547

“Controlled-release oxycodone administered every 12 hours provides effective and tolerated pain control,” minimizes the risks associated with OxyContin. “Opioid therapy is well tolerated by patients. Nevertheless, the phrase ‘Well Tolerated’ has been deleted.”

Overstatement of Efficacy

- Purdue does not understand the basis for the complaint about the plumber, “the photograph of the plumber has been changed in an effort to portray more clearly a person who as persistent, moderate to severe pain.”

Unsubstantiated Claims

- As to the qualify of sleep comment, Purdue does not agree. Nevertheless, the claim was removed.
- Purdue does not agree with DDMAC’s statement on managing breakthrough pain. “The management of breakthrough pain is discussed extensively in various guidelines referenced in the OxyContin package insert. The sentence ‘Manage breakthrough pain, if necessary with immediate-release opioid medications’ has been deleted.”
- Purdue does not agree with DDMAC’s comment on the claim, “management of side effects enhances compliance.” “Treating physicians know that management of side effects enhance compliance. Nevertheless, the phrase ‘management of side effects enhances compliance’ has been deleted.”
- Purdue also did not agree with DDMAC’s comment on the proven efficacy of OxyContin in cancer, low back pain, and osteoarthritis. “OxyContin has been shown to be effective in these clinical settings. Nevertheless, the above noted claim has been deleted and replaced with the following two bullet points: clinically proven efficacy in

			<p>moderate to severe pain; appropriate for use in moderate to severe pain when associated with cancer, low back pain, and osteoarthritis.”</p> <p>Fair Balance</p> <ul style="list-style-type: none"> The following language was added under Usage: “OxyContin, like other opioids, has been diverted for non-medical use. Careful record keeping of prescribing information, including quantity, frequency and renewal requests is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioids.” 	
OxyContin	10/25/2001	To FDA	Submission of Titration Scratch Pad for review	PDD1501610320 at 281
OxyContin	11/7/2001	To FDA	Contents Not Reported	Bates Unavailable
OxyContin	11/26/2001	To FDA	Contents Not Reported	Bates Unavailable
OxyContin	11/28/2001	To FDA	Submission of the following OxyContin promotional items for review: Drug Enforcement Admin/Natl Health Organization Joint Statement on 10/23/01: “Drug Enforcement Admin, 21 Health Groups Call for Balanced Policy on Prescription Pain Medications Like OxyContin, Revised Conversion Reference Guide, Laminated Conversion Card, Literature Reprint: “Drug Decisions for Patients with Chronic Noncancer Pain” by Gregory Holmquist, Revised Titration Guideline Card, Revised Visual Aid, ONS Questionnaire [Quiz Pad], Stickers, New Corporate Website Newsroom	PDD8013009947
OxyContin	12/6/2001	To FDA	Submission of Literature Reprint: “Recognizing and Preventing Medication Diversion” by B. Eliot Cole and Revised OxyContin vs. Acting Opioids Visual Aid	PDD1501610320 at 299
OxyContin	12/18/2001	From FDA	DDMAC responds to Purdue’s request for comments from 11/7/01 and 11/26/01 for their proposed website. DDMAC had no objections.	PURCHI-000683822
OxyContin	12/27/2001	To FDA	Submission of Managed Care Time Principles Template/Binder Page, Managed Care: OxyContin Titration Information White Paper, and “When It’s Time to Consider” Visual Aid	PDD1501610320 at 345

OxyContin	1/8/2002	From FDA	Contents Not Reported	Bates Unavailable
OxyContin	1/17/2002	Call with FDA	Call with DDMAC to see if it would be acceptable to submit advertising and promotional labeling in electronic format.	PURCHI-000685395
OxyContin	1/23/2002	To FDA	Submission of Clinical Compendium Binder ["Clinical Updates in Pain Control"], Managed Care Conversion Template and Binder Page, New Cheville Backgrounder: "OxyContin (oxycodone HCL controlled-release) Tablets CII in Post-op Pain Management and Rehabilitation"	PDD1501610320 at 393
OxyContin	2/1/2002	To FDA	Submission of Abbott Labs Piece "Take a Closer Look at OxyContin" Brochure	PDD8013012777
OxyContin	2/4/2002	Call with FDA	Contents Not Reported	Bates Unavailable
OxyContin	2/7/2002	To FDA	<p>Letter from Purdue to DDMAC regarding the 2/4/02 phone call on "Direct to Consumer" advertising of OxyContin in a poster from Montgomery General Hospital in Maryland. DDMAC "indicated that the alleged poster states 'Is your pain medication failing you? If so, talk to your nurse or doctor about OxyContin.'"</p> <p>Purdue indicates that Purdue does not promote direct to consumer with any OxyContin advertising. "Nevertheless, in order to comply with your request for a written response, we sent one of our own representatives to investigate this accusation...In conclusion I would like to reiterate that this poster was provided by PPLP in support of the JCAHO standard as part of our Partners Against Pain program, and, consistent with all of the Partners Against Pain materials, makes no specific product mention."</p>	PURCHI-000689442
OxyContin	2/11/2002	To FDA	Submission of 2002 Pain Management Prescribing Guide	PDD8013012869
OxyContin	2/15/2002	To FDA	Submission of the following OxyContin promotional items for review: Revised PCA Conversion Wall Chart, Revised Oral Opioid Wall Chart, Revised Titration Scratch Pad, Sales Aid Overheads, Revised Fast Onset Flash Card	PDD8013013042
OxyContin	3/5/2002	From FDA	DDMAC's response to Purdue's letter dated 2/7/02. DDMAC considers the matter closed.	PURCHI-000695029
OxyContin	3/6/2002	To FDA	Submission of the following OxyContin promotional items for review: Kiosk Software, Managed Care "Why OxyContin"	PDD8013013354

			Fact Sheet (Ceiling Dose) Template and Binder Page, 2/4/02 Press Release “OxyContin Lawsuit Dismissed in Mississippi; Federal Court in Kentucky Refuses Plaintiffs’ Motion to Send Case Back to State Court,” Quick Conversion Slim Jim, Partners Against Pain 0-10 Pain Scale	
OxyContin	3/19/2002	To FDA	Submission of Translight Using the Knee Image and Hip Image artwork, Q12H Flashcard “Leave Behind” for review	PKY181398114
OxyContin	4/5/2002	To FDA	Submission of the following OxyContin promotional materials for review: Partners Against Pain Quest OxyContin “Convenient Dosing” Letter, Partners Against Pain Quest OxyContin “Around-the-Clock Pain Control” Letter, Partners Against Pain Quest OxyContin “Appropriate for Such Conditions as...” Letter, Partners Against Pain Quest OxyContin “Single Entity No Aspirin or Acetaminophen” Letter, Partners Against Pain Quest OxyContin “Titration to Effective Dose” Letter, Cheville Backgrounder “OxyContin (oxycodone HCl controlled-release) Tablets CII in Post-op Pain Management and Rehabilitation,” OxyContin Patient Package Insert, OxyContin Titration “Leave Behind” Brochure, price list	PDD8013013658
OxyContin	4/22/2002	To FDA	Submission of 2002 Pain Management Prescribing Guide and price list for review	PDD8013013912
OxyContin	5/1/2002	To FDA	Submission of the following OxyContin promotional materials for review: Managed Care: Revised Rehab Patient Long-Term Care Case Study, Managed Care: Revised Long-Term Case Study – Musculoskeletal Pain, Binder Page for Managed Care White Paper, Press Release dated 3/28/02 entitled “Prescription Protection Program Offered to Arkansas Physicians” and the same press release for Louisiana, Massachusetts, Missouri, and Oregon, price list	PDD8013014288
OxyContin	5/17/2002	To FDA	Submission of the following OxyContin promotional materials for review: Letter to Pharmacist to Introduce the OxyContin Patient Information Sheet, Wall Chart: Skeletal Depiction of the Knee, OxyContin Sheet: AdvancePCS Performance Drug List, “Take a Closer Look at OxyContin” Brochure, OxyContin Ceiling List, and price list	PDD8013014598

OxyContin	5/29/2002	Call with FDA	DDMAC requested the protocol and full statistical plan used to support the study discussed in the Cheville Backgrounder [Purdue Artwork Number B6925, entitled “OxyContin (oxycodone HCL controlled-release) Tablets CII in Post-op Pain Management and Rehabilitation”] “I explained that this piece was derived from a published article and that the study was not conducted, written or paid for by Purdue; and, therefore, PPLP did not have access to those documents.”	PURCHI-000697655
OxyContin	5/29/2002	To FDA	PPLP submitted an article titled “A Randomized Trial of Controlled-Release Oxycodone During Inpatient Rehabilitation Following Unilateral Total Knee Arthroplasty” in support of their Cheville Backgrounder.	PURCHI-000697505
OxyContin	6/24/2002	To FDA	Purdue submitted a letter to DDMAC for a new visual aid, promoting Avinza... “In the promotional labeling for Purdue Pharma LP (PPLP) products have boxed warnings (which were submitted to your Division for comment prior to dissemination), we understood that DDMAC required the boxed warnings to be prominently featured in the text of the promotion. As it relates to prominence, we also understood that this meant exactly as it appears in the package insert, within a prominent boxed border and entitled ‘WARNING’”. Purdue points to a new visual aid for Avinza where the warning is presented without a box and without the title “WARNING.” It also does not refer to it as a boxed warning. Purdue also mentions a direct-to-consumer promotion...“which Janssen pays pharmacists to enclose prescriptions filled for OxyContin Tablets and other oral opioid products. Again the boxed warning is featured in this space without the border.” “Please advise us whether it is the policy of DDMAC to require the use of the boxed border and the caption of ‘WARNING’ as it appears in the package insert, as part of the prominence of such a warning in promotional labeling.”	PURCHI-000698984

OxyContin	7/12/2002	To FDA	Submission of Hospital Display Panel, Managed Care: Revised Long-Term Care Handbook, Abbott Labs "Take a Closer Look at OxyContin" Femoral Break Case Study, and price list for review	PDD8013015820
OxyContin	8/15/2002	To FDA	Submission of the following OxyContin promotional materials for review: Letter to Wholesalers Announcing New OxyContin Patient Information Sheet, Wall Chart: Skeletal Depiction of the Back, Issue of "Do Not Net Guide" Regarding Pain Management, sponsored by Purdue (Partners Against Pain), Patient Information Sheet (Spanish), "Take a Closer Look at OxyContin" Brochure, New Mailing: The Relief Paradigm Long-Term Care In-Service, price list	PDD8013017053
OxyContin	9/4/2002	To FDA	Submission of the following OxyContin promotional materials for review: "Take a Closer Look at OxyContin" Visual Aid, Managed Care: Long-Term Care Handbook, Managed Care: Long-Term Care Competition Visual Aid, Abbott Labs "Take a Closer Look at OxyContin" Slim Jim, "When it is Time to Consider Q4-6H Opioids" Visual Aid, price list	PDD8013017556
OxyContin MS Contin	9/13/2002	To FDA	Submission of Booklet: American Pain Society's "Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis"	PDD8013017810 PDD8023092491
OxyContin	10/10/2002	To FDA	Submission of the following OxyContin promotional materials for review: Q12H "Leave Behind" Flash Card, Managed Care: Long-Term Care Competition Visual Aid, Hip Fracture Case Study (Abbott), "Patients in Pain" Video by Dr. Neil Irick, price list	PDD8013018509
OxyContin	10/24/2002	To FDA	Submission of Partners Against Pain New Complete Pain Management: Conversion Case Studies Slide Kit, Partners Against Pain New Opioid Conversion Complete Pain Management Self Assessment Case Studies, Abbott Labs OxyContin Femur Fracture Case Study, price list for review	PDD8013018828
OxyContin	11/4/2002	To FDA	Submission of "There Can Be Life with Relief" Visual Aid, Law Enforcement Transmittal Memo ("Purdue Bulletin for Law Enforcement Officers, Volume 1: 'Useful Facts About Pain Medications'" issued 10/2, price list for review	PDD8013019210
OxyContin	11/14/2002	To FDA	Submission of Wall Cart re: Hip, Ceiling Reference Card, and price list for review	PDD8013019491

OxyContin	1/10/2003	Meeting with FDA	Discuss warning letter	Bates Unavailable
OxyContin	1/10/2003	To FDA	Submission of Medicaid Position Papers: "OxyContin Tablets – Therapy for Persistent Pain: Clinical Issues Rationale, & Management Strategy," and price list for review	PDD8013020843
OxyContin	1/13/2003	Call with FDA	Purdue left a message for Thomas Abrams stating that PPLP's response to the 12/24/02 DDMAC letter would be provided by 1/14/03.	PURCHI-000707061
OxyContin	1/13/2003	To FDA	Submission of Journal Ad: "When It's Time to Consider Q4-6H Opioids...", Journal Ad: "There Can Be Life With Relief," and price list for review	PKY181396671
OxyContin	1/14/2003	To FDA	PPLP (written by counsel) To FDA in response to the warning letter and meeting held on 1/10/2003. Same as letter dated 1/13/2003 (see above under Purdue Response to Warning Letter for summary)	PURCHI-000711057
OxyContin	1/28/2003	From FDA	Response to PPLP's 1/14/2003 submission. DDMAC reviewed the materials to determine if they supported PPLP's claims that the Warning Letter shouldn't have been issued. <ul style="list-style-type: none"> "We are not persuaded by the arguments presented in your letter...We have determined that the Warning Letter is, from both a legal and policy perspective, the appropriate regulatory response to the Ads, and is factually accurate and appropriate in tone." <p>Reliance on General Reference to Boxed Warning in Brief Summary</p> <ul style="list-style-type: none"> "...we are not persuaded that Purdue acted reasonably in using a general reference to the boxed warning in the brief summary of the Ads and failing to prominently disclose the specific, potentially fatal risks associated with OxyContin in the body of the Ads." "In addition, we believe that it is widely known and accepted that the most serious risks associated with a drug (especially potentially fatal risks as noted in a boxed warning) must be 	PKY181712931

prominently included in all promotion, including journal ads.”

Sufficiency of Risk Information Presented

- “Your letter also argues that Purdue’s presentation of risk and indication information in the body of the Ads was ‘sufficiently prominent.’ We are not persuaded.”
- “Your letter also states that the Ads highlight that the product ‘can cause respiratory depression’ which, you state is ‘*the* essential, inherent risk’ associated with the drug...It is important to note, as discussed in our Meeting, that OxyContin poses additional, more serious risks than other opioids.”
- “Specially, due to its controlled-release formulation, if an OxyContin tablet is broken, chewed, or crushed, it can release a fatal dose of the drug...When this specific, important information is not conveyed, general reference to the risk of respiratory depression with opioids as being the most serious risk becomes misleading in failing to give an accurate picture of the safety profile of OxyContin with its more serious, potentially fatal risks.”
- “Furthermore, we are not persuaded by your argument that having ‘CII’ as part of the drug name logo in Ads sufficiently conveys the important safety information from the boxed warning related to the abuse liability of OxyContin.”

Suggestion of Broad Usage/Lack of Indication Information in the Ads

- “We are also not persuaded by your statement that the Ads effectively communicate the limitations on the indications for OxyContin.”
- “Purdue also disputes the need for disclosure of the additional limitations related to the indicated

use of OxyContin...We maintain our position that this information is necessary because of the broad claims presented in the body of the Ads, which suggest broad use of OxyContin for pain relief..."

"Change of Opinion" Argument

- "We also do not believe that the violations cited in the Warning Letter reflect a 'change of opinion' on DDMAC's part. DDMAC was never asked by Purdue for advisory comments on the Ads or any similar advertisements. The promotional materials cited in your letter that were reviewed by DDMAC at Purdue's request included the appropriate risk information and other contextual information, thus distinguishing them from the Ads."
- "We also do not believe that the Warning Letter represents a change of opinion related to the presentation of risk information for OxyContin...It is crucial to note that the previous pieces reviewed by DDMAC prominently included the language from the boxed warning about the specific fatal risks associated with OxyContin, along with those more general statements about opioids, thus placing them in appropriate context."

Belief that the Ads were Consistent with 2001 Correspondence/Contacts with the Agency

- "As noted above, a substantial portion of Purdue's argument in the Meeting and in your letter states a perceived lack of adequate 'guidance' that disclosure of the most important risk information from the boxed warning needed to be included in the body of the Ads. Purdue states that it believed that the Ads were consistent with the correspondence and contacts with the Agency in 2001, at the time the boxed warning was added to the OxyContin PI. We

			<p>believe, on the contrary, that the Agency's communications on this issue were clear and do not support such an interpretation...Purdue was given specific oral and written guidance that the boxed warning risk information, information on the drug's abuse potential, and the indication information were to be prominently included in <u>all</u> promotional materials."</p> <p>Appropriateness of Issuing a Warning Letter</p> <ul style="list-style-type: none"> • "Finally, your letter questions whether the Agency needed to issue any 'official correspondence' for the violations in the Ads. DDMAC re-reviewed the Warning Letter using the criteria it applies when considering whether to send a Warning Letter. DDMAC concluded once again that issuance of a Warning Letter concerning the Ads was warranted." <p>Conclusion</p> <ul style="list-style-type: none"> • "In conclusion, we believe that issuing the Warning Letter was warranted and that its language accurately and appropriately reflects the violations in the Ads and the Agency's serious concerns with respect to these Ads." 	
OxyContin	1/29/2003	Call with FDA	Contents Not Reported	Bates Unavailable
OxyContin	1/29/2003	From FDA	<p>FDA's response to PPLP's 1/24/03 response to the Warning Letter (see above under Company Response to Warning Letters).</p> <ul style="list-style-type: none"> • "We disagree with your position that the Warning Letter is inconsistent with the law or represents a new interpretation of the requirements of prescription drug advertisements. • "We also maintain that the violations cited in the Warning Letter raise significant public health concerns." • "In addition, we do not believe that your proposed plan to discontinue the Ads and disseminate the 	PDD8003065502

			advertisement attached as Exhibit C to your letter adequately addresses the concerns expressed in the Warning Letter and the need for dissemination of accurate and complete information to correct your Ads.	
OxyContin	1/30/2003	To FDA	<p>PPLP's submission to the FDA following the 1/29/03 phone call, attaching the proposed text for the corrective advertisement. "The ad would be three pages. The first page would be the 'Dear Healthcare Practitioner' letter, the second page would include the full indication and the boxed warning, and the third page would be the brief summary..."</p> <p>PPLP Proposed DHP Letter "Earlier publications of this journal contained advertisements for OxyContin...that were the subject of a Warning Letter from the U.S. Food and Drug Administration's Division of Drug Marketing, Advertising, and Communications. The Warning Letter stated that information concerning important risks associated with OxyContin Tablets that appeared in the boxed warning in the brief summary section of the ads, were not featured in the main body of these advertisements. The Warning Letter also stated that the box of the ads did not feature the potentially fatal risks associated with the use of OxyContin Tablets and the abuse liability of OxyContin Tablets, which is a Schedule II controlled substance. Consequently, we direct you to the information on safety, risks, and indications for OxyContin Tablets, including the boxed warning, located on the adjacent page."</p>	PDD8003063623
OxyContin	1/31/2003	From FDA	<p>FDA's response to PPLP's 1/30/03 submission. "We believe certain modifications are needed to properly communicate the intended message of these corrective advertisements. Therefore, we propose the attached revised text for the 'Dear Healthcare Practitioner' letter portion of the advertisement."</p> <p>FDA's Proposed DHP Letter "Earlier publications of this journal contained advertisements for OxyContin...that were the subject of a</p>	PDD8003065498

			Warning Letter from the U.S. Food and Drug Administration in January 2003, stating that the advertisements violated provisions of the drug advertising and promotion regulations. The Warning Letter stated that information concerning important risks associated with OxyContin Tablets that appears in the boxed warning of the OxyContin Prescribing Information was not presented in the main body for the advertisements. This information concerns potentially fatal risks associated with the use of OxyContin and the abuse liability of OxyContin. In addition, the Warning Letter stated that the body of the advertisements did not present information regarding limitations on safety, risks, and indications for OxyContin Tablets, including the boxed warning, located on the adjacent page.”	
OxyContin	2/4/2003	To FDA	Purdue submitted a corrective “Dear Healthcare Practitioner” ad for review.	PURCHI-000707528
OxyContin	2/13/2003	To FDA	Following the January 10, 2003 meeting to discuss the draft journal articles, PPLP submitted mock-ups of a conversion/titration guide, conversion guide, titration guide, detail aid, flash card, one-page journal ad, two-page journal ad, and two patient profiles for review.	PURCHI-000708826
OxyContin	2/21/2003	To FDA	Submission of the following OxyContin promotional materials for review: Press Release dated 1/22/03 entitled “Purdue Statement on DDMAC Warning Letter,” Press Release dated 1/2/03 entitled “OxyContin Case Against Purdue Pharma Dismissed by California Judge; Claims of Inadequate Warning and Aggressive Marketing Barred from State Court,” Press Release dated 1/23/03 entitled “Purdue Pharma will Replace OxyContin (oxycodone HCL controlled-release) Tablets Stolen from Pharmacies,” Purdue Pharma Medical Education Resource Catalog – Issue 1, January 2003, and price list	PDD8013021774
OxyContin	2/24/2003	To FDA	Submission of Booklet: “Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis,” Second Edition, 2002 American Pain Society, and price list	PDD8013021946
OxyContin	3/6/2003	To FDA	Purdue’s letter to the FDA following a discussion earlier that day on a planned publication of a corrective advertisement.	PDD1501615565

			PPLP will run the ad for April, May and June.	
OxyContin	3/10/2003	To FDA	Submission of Journal Ad dated January 2003 entitled "Important Correction of Drug Information," Press Release dated 2/25/03 entitled: "Five OxyContin Cases Against Purdue Pharma Dismissed – Purdue Hails Benefit to Patients in Lawsuits Dismissed in West Virginia, Kentucky, Texas and Utah"	PDD8013022539
OxyContin	3/11/2003	Call with FDA	Contents Not Reported	Bates Unavailable
OxyContin	3/12/2003	To FDA	PPLP advises the FDA that since the 1/10/03 meeting their sales force has been promoting with only a package insert. PPLP enclosed the references for the draft promotional materials requested by the FDA on 3/11/03.	PURCHI-000709052
OxyContin	3/13/2003	To FDA	Contents Not Reported	Bates Unavailable
OxyContin	3/26/2003	From FDA	<p>Response from the FDA to PPLP's submission on 2/13/03 request for comments on proposed promotional materials.</p> <p><u>Detail Aid</u></p> <p>Communication of Indication</p> <ul style="list-style-type: none"> • "The cover page for your detail aid presents as its first claim 'For patients with persistent pain...' This claim is misleading because it implies that all patients with persistent pain are appropriate candidates for OxyContin." • "Your detail aid is misleading because your selective presentation of OxyContin's indication on various pages does not adequately convey that the statements presented constitute OxyContin's indication and its limitations for use. We suggest that you present OxyContin's entire indication with its limitations contiguously...we suggest that you prominently present the complete indication before, or in conjunction with your initial claims of efficacy for OxyContin to more adequately convey to healthcare professionals which patients are appropriate candidates for OxyContin therapy." <p>Misleading Efficacy Claims</p> <ul style="list-style-type: none"> • Claim: "Life with Versatility" – "misleading because it implies that 	PURCHI-000709630

OxyContin will allow a patient's life to be more versatile when such has not been demonstrated by substantial evidence."

- Claim: "Appropriate for use in moderate to severe pain when associated with conditions such as...postoperative pain." – "misleading because it implies that all patients with postoperative pain are candidates for OxyContin when such is not the case."
- Claim: "Pain reduction in placebo-controlled, fixed-dose trial of patients with moderate to severe osteoarthritis pain (n=133)." – "misleading because (1) the y-axis as presented distorts or misrepresents the distance between the 4-point categorical scale (i.e., 0, 1, 2 and 3) for 'Mean Pain Intensity' and "you omitted appropriate context (legend) for interpreting 'Mean Pain Intensity' of 1 and 2."
- Claim: "Life With Stable Relief" followed by the claim 'Avoid serum concentration peaks and valleys.' – "Implication that OxyContin is more efficacious than immediate-release oxycodone is misleading because such has not been demonstrated by substantial clinical evidence..."
- Claim: "A variety of dosage levels' along with a chart entitled 'Percentage distribution of cancer patients after 12 weeks of treatment with OxyContin, by total daily dose (n=86).' – "Because you have not submitted the corresponding protocols and clinical study reports in their entirety we can not comment on this presentation at this time."

Minimization of Risk

- Presentation: Boxed Warning and part of indication on page titled "Life with relief." – "misleading because it minimizes the serious and life-threatening risks associated with OxyContin."
- Claim: "Well-tolerated opioid therapy" – "misleading because it

			<p>minimizes the serious and potentially life-threatening risks associated with OxyContin therapy.”</p> <ul style="list-style-type: none"> • Presentation: “OxyContin is a Schedule II controlled substance with an abuse liability similar to morphine...” is located under the header, ‘Effective therapy when used properly.’ – “misleading because it minimizes the importance of the risk.” • Presentation: “Adverse events are dose-dependent, and their frequency depends on dose, clinical setting...” – “misleading because it implies this claim applies to all adverse events, including the serious adverse events, when such is not the case.” • Claim: “OxyContin 80 mg tablets are for use in opioid-tolerant patients only” – “DDMAC notes that you do not actively promote the use of the 160 mg dose tablet of OxyContin in this promotional piece. However, the 160 mg dose tablet is available and you do promote using OxyContin in dosages beyond 160 mg...Therefore, this presentation is misleading because it omits the possible risk of fatal respiratory depression associated with the 160 mg dosage strength in opioid naïve patients.” <p>Dosing and Administration</p> <ul style="list-style-type: none"> • “You present a reasonable starting dose of OxyContin on page 10 as ‘2x 10 mg q12h’ for Vicodin 2x 5 mg q6h = 40 mg hydrocodone/day. This is presentation is misleading because it suggests a higher dosage of OxyContin than is recommended based on the conversion guidelines set forth in the Dosage and Administration section of the PI.” <p>General</p> <ul style="list-style-type: none"> • Claim: “Pain in the immediate postoperative period...for patients not previously taking OxyContin” – “DDMAC suggests adding additional context to this and similar 	
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claims...consistent with the PI, which states ‘because its safety in this setting has not been established.’”

Conversion/Titration Guide
Misleading Safety Presentation

- “You present OxyContin’s common side effects, contraindications, etc. under the header titled ‘Safety Information.’ This presentation is misleading because it implies that the information you present under this header constitutes all of the safety information associated with the use of OxyContin when such is not the case. Therefore, we recommend you revise the header to ‘Additional Safety Information.’”

Two Patient Profiles
Minimization of Risk

- “You present your efficacy claims for OxyContin on the front of the one-page patient profiles and the boxed warning and other important risk and indication information on the back. This placement of important risk and indication information lacks prominence and does not adequately communicate the serious risks and prescribing issues associated with the use of OxyContin, needed to provide appropriate context and balance for your claims...”
- Claim: “OxyContin is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. See CONTRAINDICATIONS in professional prescribing information.’ This presentation...minimizes the serious and life-threatening risks associated with OxyContin by not disclosing these specific situations where OxyContin is contraindicated.”
- “...you fail to present important risk information from the PI. Specifically, you fail to present the statement ‘OxyContin is not indicated for pre-

			emptive analgesia..."	
OxyContin	3/28/2003	To FDA	Submission of Booklet: Purdue's "2003 Pain Management Prescribing Guide" for review	PDD8013023374
OxyContin	4/2/2003	To FDA	<p>Letter from Purdue advising DDMAC that in reviewing their records it appeared that some print journal advertisements had not been submitted at the time of dissemination.</p> <p>Purdue submitted the following journal advertisements: Press release 10/28/01: "Reports Confirm Most Overdose Deaths Caused by Abuse of Multiple Drugs," Press Release 11/20/01: "Purdue Pharma Begins Shipment of Specially Marked OxyContin Tablets to Mexico and Canada," Press Release 12/3/01: "Purdue Pharma Begins Clinical Studies of Abuse-Resistant Pain Medication," Press Release 1/2/02: "Federal Judge in Kentucky Rejects Injunction on OxyContin," Press Release 1/7/02: "Plaintiffs in Maine and North Carolina Voluntarily Dismiss OxyContin Lawsuits," Press Release 2/4/02: "OxyContin Lawsuit Dismissed in Mississippi; Federal Court in Kentucky Refuses Plaintiffs' Motion to Send Case Back to State Court," "Statement of Dr. Paul D. Goldenheim on Behalf of Purdue Pharma L.P. Before the Committee of Health Education, Labor, and Pensions, U.S. Senate 2/12/02," Press Release 2/28/02: "Class Action Denied in Kentucky OxyContin Litigation; Judge Rules that Plaintiffs Failed All Legal Tests," Press Release 4/16/02: "Purdue Pharma Disputes DEA Analysis of Medical Examiner Reports," Press Release 4/24/02: "Four More Purdue Pharma Victories in OxyContin Litigation," Press Release 4/25/02: "Purdue Pharma Statement on Stop & Shop Decision to Stop Stocking OxyContin," Press Release 5/6/02: "Purdue Pharma Applauds New Ethical Marketing Code Adopted by PhRMA," Press Release 6/18/02: "Purdue Pharma Provides Update on Development of New Abuse-Resistant Pain Medications," Press Release 6/26/02: "Another Legal Victory for Purdue Pharma in OxyContin Litigation," Press Release</p>	PDD8003222935

			<p>6/27/02: "Purdue Pharma Implements National Surveillance System to Track Diversion and Abuse of Controlled Pain Medications," Press Release 8/5/02: "Legal Victories for Purdue Pharma Mount in OxyContin Litigation," Press Release 8/22/02: "West Virginia Judge Dismisses OxyContin Case Against Purdue Pharma," Press Release 9/23/02: "OxyContin Case Against Purdue Pharma Dropped in Los Angeles," Press Release 10/3/02: "OxyContin Case Against Purdue Pharma Dismissed in Ohio," Press Release 10/23/02: "Class Certification Denied in Kentucky OxyContin Litigation Against Purdue Pharma," Press Release 12/4/02: "Thousands of Counterfeit OxyContin Tablets Seized by U.S. Customs Service," Press Release 1/2/03: "OxyContin Case Against Purdue Pharma Dismissed by California Judge; Claims of Inadequate Warning and Aggressive Marketing Barred from State Court," Journal Ad: "24 Hours of Oxycodone Pain Control – The Old Way," Journal Ad: "24 Hours of Oxycodone Pain Control – The Hard Way," Journal Ad: "24 Hours of Pain Control – The Easy Way," Journal Ad: "24 Hours of Pain Control – The Easy Way" (general), Journal Ad: "24 Hours of Pain Control – The Easy Way" (AIDS), Journal Ad: "24 Hours of Pain Control – The Easy Way" (long-term care), Journal Ad: "24 Hours of Pain Control – The Easy Way" (anesthesia), Journal Ad: "24 Hours of Pain Control – The Easy Way" (rheumatology), Journal Ad: "24 Hours of Pain Control – The Easy Way" (surgery), Journal Ad: "Proven Effective in Arthritis Pain," Journal Ad: "Proven Effective in Low Back Pain," Journal Ad: "Proven Effective in Post-Op Pain," Journal Ad – General Ad, Journal Ad: "Opioids – Separating Myths from Facts," Journal Ad: No Claims, Journal Ad: Partners Against Pain General Ad, Journal Ad: "Don't Complicate Pain Relief...Keep it Simple," Journal Ad: Partners Against Pain – General Ad, Journal Ad: General Ad to Introduce 160 mg Strength Tablet, Journal Ad: "Effective in Low Back Pain," Journal Ad: "Effective in Post-Op Pain," Journal Ad: "Partners Against Pain – General Ad," Journal Ad: Two Cup Ad, Journal Ad:</p>	
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			<p>“Protect Your Practice – Free Tamper-Resistant Rx Pads for Prescribing Controlled Substances,” Journal Ad: No Claims Ad, Journal Ad: “Partners Against Pain – Thoughts on Pain,” Journal Ad: “For 12 Hours of Sustained Analgesia, Take a Closer Look at OxyContin,” Journal Ad: “When It’s Time to Consider Q4-Q6H Opioids,” Journal Ad: Purdue & the APhA Announcing a 10-Point Program to Combat Prescription Drug Abuse, Journal Ad: “There Can be Life with Relief” (fish ad – one page), Journal Ad: “There Can be Life with Relief” (fish ad – spread)</p>	
OxyContin	4/16/2003	To FDA	PPLP’s response to the DDMAC comments on 3/26/03. PPLP submitted draft mock-ups that incorporated the comments from the 3/26/03 letter.	PURCHI-000710690
OxyContin	4/22/2003	To FDA	Submission of Goniometer with OxyContin logo (Abbott) and Current Purdue Wholesaler Pricing Schedule for OxyContin for review	PDD8013024383
OxyContin	4/25/2003	To FDA	<p>Purdue’s letter to the FDA referencing their letter from 4/2/03 with the submission of the journal advertisements and press releases not previously submitted. Purdue contacted Abbott to obtain any additional promotional items not previously submitted. Abbott found one journal advertisement that is no longer in circulation.</p> <p>Submission of the Journal Ad – “Getting Around the Ups and Downs of Postoperative Pain Management”</p>	PDD8003223076
OxyContin	5/8/2003	To FDA	Submission of “Dear Healthcare Professional” Letter specifically about OxyContin to be distributed with the American Pain Society’s “Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis and Juvenile Chronic Arthritis,” Second Edition, 2002, and Current Purdue Wholesaler Pricing Schedule for review	PDD8013025003
OxyContin	5/23/2003	From FDA	<p>DDMAC’s response to PPLP’s submission of draft mock-ups from 4/16/03.</p> <p><u>Detail Aid Context</u></p> <ul style="list-style-type: none"> • “We note that you have revised your 	PURCHI-000719431

			<p>pharmacokinetic presentation, which compares the plasma concentrations of OxyContin and immediate-release oxycodone over time on page 9 of the detail aid. We suggest adding the material fact ‘In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and Cmax, and similar to Cmin (through) concentrations’ necessary to provide adequate context in light of the representations you make regarding OxyContin exhibiting less fluctuations in plasma concentrations than immediate-release oxycodone.</p> <p><u>Titration Guide</u> Minimization of Risk</p> <ul style="list-style-type: none"> • “You present important risk information (e.g. most serious risk, contraindications, and common side effects) under a header entitled ‘There can be life with relief.’ This presentation of risk information under a heading of efficacy is misleading because it minimizes the importance of the risk. We suggest that you place this important information under a header that clearly communicates the nature of this risk information.” 	
OxyContin	6/20/2003	To FDA	<p>Submission of the following promotional materials for review: Testimony given by Purdue Speaker Lynda Nelson Gardner to the Dept. of Human Services in Opposition to Proposed Amendments to OAR 410-121-0030, the Practitioner-Managed Prescription Drug Plan (PMPDP), Presentation given by Purdue Speaker Robin Hogen entitled: “Victimized Twice: Collateral Damage from the Controversy Surrounding OxyContin,” Presentation by Purdue Speaker Michael Friedman entitled: “Corporate Citizenship: Addressing Prescription Drug Abuse through Community Involvement,” Presentation by Purdue Speaker Dr. Howard Heit, entitled “Addiction: What is it and What are its Implications regarding the Treatment of the Pain Patients?”, Presentation by Purdue</p>	PDD8013026296

			<p>speaker Dr. Rupa Shah, entitled “Pain Management 101,” Opinion Editorial text to [appear in a medical journal] entitled “Lawsuits can be Bad Medicine” by Howard Udell of Purdue, Press Release 5/15/03 entitled “Six More OxyContin Lawsuits Against Purdue Pharma Dismissed,” Agency for Health Care Policy and Research’s “Quick Reference Guide for Clinicians, Number 9: Management of Cancer Pain: Adults,” OxyContin Visual Aid: “There can be Life with Relief,” OxyContin Conversion/Titration Guide: “There can be Life with Relief,” OxyContin Titration Guide: “There Can be life with Relief,” OxyContin Conversion Guide: “There can be Life with Relief,” and Current Purdue Wholesaler Pricing Schedule for OxyContin</p>	
OxyContin	7/2/2003	From FDA	<p>DDMAC advises PPLP that as part of its routine monitoring and surveillance program, they have reviewed and have some concerns with a promotional visual aid for OxyContin that was disseminated at The American Society of Clinical Oncology (ASCO) 2003 Annual Meeting.</p> <p>“DDMAC has reviewed this promotional visual aid and is concerned about its content. Therefore, DDMAC requests that Purdue investigate the extent to which this promotional visual aid has been disseminated...DDMAC also requests that Purdue provide a complete explanation to us regarding the circumstances of all such dissemination.”</p>	PURCHI-000720619
OxyContin	7/7/2003	To FDA	<p>PPLP reports an error in the visual aid submitted on 6/20/2003 and notifies DDMAC that they will be destroying the inventory and reprinting.</p>	PURCHI-00720344
OxyContin	7/10/2003	To FDA	<p>Letter from Purdue proposing the addition of a sentence to the promotional materials approved on 5/23/03 and the draft materials submitted on 4/16/03. Purdue wants to include the following sentence: “As used here, ‘moderate’ and ‘moderate to severe’ pain does not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort.”</p> <p>“We believe that the current labeling for OxyContin Tablets is clear and appropriate.</p>	PDD8013027455

			The proposed text addition provides specific examples of conditions in which the use of OxyContin Tablets is not appropriate.”	
OxyContin	7/17/2003	To FDA	Submission of Slide Kit: “Lawful Prescribing and Prevention of Diversion, Edition 2; 2003,” Strategizer Brochure of the Community Anti-Drug Coalitions of America: “Prescription Drug Abuse Prevention – Where Do We Go From Here,” and Current Purdue Wholesaler Pricing Schedule for OxyContin	PDD8013027660
OxyContin	7/18/2003	To FDA	PPLP submits draft mock-ups to the FDA for review including: <ul style="list-style-type: none"> • ABBOTT detail aid including two patient profiles inside pocket • Convention panels (total of 6) • Four page brochure • Smaller four page brochure with pocket intended to hold a package insert 	PURCHI-000722699
OxyContin	7/22/2003	To FDA	Submission of Two-Page Fishing Ad: “There can be Life with Relief” and Current Purdue Wholesaler Pricing Schedule for OxyContin for review	PDD1501129749
OxyContin	7/25/2003	To FDA	PPLP submits a Budget Impact Model (BIM) for the management of moderate to severe pain. The BIM is a computer program designed to produce tailored analyses of potential pharmacy costs.	PURCHI-000721227
OxyContin	8/1/2003	To FDA	Submission of Press Release 8/8/01: International Patent Application to be Published on Abuse-Resistant Pain Reliever being Developed by Purdue Pharma,” One-Page Fishing Ad: “There can be Life with Relief,” Current Wholesaler pricing schedule for review	PDD8013028913
OxyContin	8/14/2003	From FDA	FDA’s response to PPLP’s 7/10/03 submission requesting comments on proposed promotional materials. Detailed Aid <ul style="list-style-type: none"> • “You present the contextual information ‘As used here, ‘moderate’ and ‘moderate to severe’ pain do not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort.’ Because this information provides additional context to OxyContin’s indications and limitations to use, we suggest that 	PURCHI-000721639

			you present this contextual information under the 'Indications and Usage' header..."	
OxyContin	8/18/2003	To FDA	Letter to the FDA calling DDMAC's attention to a violation of 21 CFR 312.7 (a) Promotion of Investigational New Drugs by Penwest Pharmaceuticals and Endo Pharmaceuticals. Both companies promoted Oxymorphone ER. "They have used these public forums to provide misleading information concerning Purdue Pharma L.P. investigational product (hydromorphone) that minimizes the safety risks associated with Oxymorphone ER."	PURCHI-000721643
OxyContin	8/21/2003	To FDA	Submission of Press Release 7/31/03: "OxyContin Cases Against Purdue Pharma Dismissed in Florida, Mississippi and West Virginia," Visual Aid: Life with Relief, Current Wholesaler pricing schedule for review	PDD8003183301
OxyContin	9/9/2003	To FDA	Submission of Presentation by Purdue Speaker Dr. D. Haddox entitled: "Autopsies in which Oxycodone was Reported: An Analysis," Press Release dated 8/20/03 entitled: "Six OxyContin Cases End in Four States," and Literature Reprint entitled: "Controlled-Release Oxycodone for Pain in Diabetic Neuropathy" by Drs. Gimbel, Richards and Portenoy, and Current Wholesaler pricing schedule for review	PDD8013029818
OxyContin	10/7/2003	From FDA	<p>FDA response to PPLP's submission from 7/18/03.</p> <p>Detail Aid</p> <ul style="list-style-type: none"> • "The cover page for your detail aid presents as its first claims 'For moderate to severe pain when continuous, around-the-clock analgesic is needed for an extended period of time; and 'Take a closer look at OxyContin'...This presentation is misleading because it implies that OxyContin is appropriate for use in all post-operative conditions when such is not the case." • "Claims of 'flexible dosing' for OxyContin are misleading because they imply that the administration for OxyContin can be varied, when such is not the case." 	PURCHI-000722973

			<p>Two Patient Profiles</p> <ul style="list-style-type: none"> “...you present important contextual information...in footnotes the bottom of the page that are very difficult to read due to their small type size. Disclosure of this important information is necessary to provide appropriate context to the aforementioned claim. We suggest that this contextual information be displayed with a comparable prominence and readability to your proposed claim.” <p>Four Page Brochure</p> <ul style="list-style-type: none"> “...you present a graph illustrating the analgesic effect of OxyContin as compared to opioid with NSAIDS/APAP (ONA) with increasing doses. This graph is misleading because it implies that OxyContin provides a greater analgesic effect than ONA prior to the ceiling effect when such has not been demonstrated by substantial evidence. This implied claim is not supported by the reference supplied to support these claims.” 	
OxyContin	10/16/2003	From FDA	FDA response to PPLP’s submission on the promotional activities of Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals for Oxymorphone ER. The FDA advises that they will be evaluating the situation.	Bates Unavailable
OxyContin	10/17/2003	To FDA	Submission of the following promotional items for review: Generic Article on Tamper-Resistant Pads, entitled: “Prescription Protection Program Offere to Prescribers,” Purdue Pharma Statement Made 9/9/03 at FDA Anesthetic and Life Support Drugs Advisory Committee Meeting, Letter from Pamela Bennett of Purdue Pharma (w/ attachments) to Barbara Walters of “The View” TV Show Regarding OxyContin, Convention Panel – “I Got My Life Back” artwork, Revised Presentation by Purdue Speaker Dr. Bill Morgan, entitled: “Pain Management in the Post-Operative Patient,” Press Release 9/18/03, entitled: “Five OxyContin Cases Against Purdue Pharma Dismissed, Revised OxyContin	PDD8013031346

			Conversion Reference Guide, Revised OxyContin Titration Guideline Card, Revised OxyContin Laminated Conversion/Titration Card, and Current Wholesaler pricing schedule for review	
OxyContin	10/29/2003	To FDA	PPLP submits the following mock-ups for review and comments: <ul style="list-style-type: none"> • OxyContin 10/20 mg Visual Aid • Three Case Studies to be inserted in the referenced Visual Aid: Osteoarthritis – Pain 1, Osteoarthritis – Pain 2, Rheumatoid Arthritis Pain • Percussion Hammer, bubble wrapped with package insert. 	PURCHI-000764097
OxyContin	11/3/2003	To FDA	Submission of the following promotional items for review: Purdue's Letter to the Editor of the CHEMICAL AND ENGINEERING NEWS in Response to a 9/15/03 Column by William Schulz Regarding Abuse of OxyContin, 2003 Convention Panel: "There Can Be Life with Relief" (Art Lady) artwork, 2003 Convention Panel: "There Can Be Life with Relief" (Blues) artwork, 2003 Convention Panel: "There Can Be Life with Relief" (Fishing-Second Version) artwork, 2003 Convention Panel: "There Can Be Life with Relief" (Black Box with Montage Art) artwork, 2003 Convention Panel: "There Can Be Life with Relief" (Reading) artwork, pricing schedule	PDD8013032375
OxyContin MS Contin	11/4/2003	To FDA	Submission of the following promotional items for review: 2005 PDR (Rx Products), schedule for OxyContin, package insert for MS Contin	PDD8003256092
OxyContin	11/4/2003	To FDA	Letter from Purdue on a promotional piece...PPLP is writing because they believe the piece contains representations that are false or misleading. DAWN Data Representation <ul style="list-style-type: none"> • There is a presentation of data from DAWN that is false or misleading. "The data suggests that the DFTS product has a unique safety profile, based on the low number and low percentage of ER visits relative to the total number of visits for all products. The presentation implies that there is a low incidence of abuse of DFTS since these mentions are for 	PDD8003185615

			<p>‘abuse’ ...”</p> <ul style="list-style-type: none"> • “This presentation makes false or misleading comparative claims that DFTS is has less abuse potential than other listed opioid products. There is no substantial evidence or clinical evidence to support a comparative claim that the DFTS product has a lower risk of abuse than the other products...is a safer opioid than the other opioids listed.” • “The presentation does not provide fair balance concerning the limitations of the DAWN data presented....” • “The relative market share of the various products is also not described. A product with a lower overall number of units sold compared to another product with a much higher number of units sold may have a lower total of ED mentions. It is false or misleading to compare the total ED mentions without any comparison of the total usage among these products.” <p>Quality of Life Claims</p> <ul style="list-style-type: none"> • “These presentations broaden the indication for DFTS since they are not balanced with the indication in the approved product labeling...” • “The studies, from which the promotional claims in this piece are based, do not appear to be referenced in the promotional piece. A search of the medical literature publications that may describe these studies...” 	
OxyContin	11/13/2003	To FDA	Submission of the following promotional items for review: 2003 Convention Panel: “There Can Be Life with Relief” (Picnic) artwork, Purdue’s Letter to the Editor of Newsweek Magazine Regarding the 10/20/03 Cover Story about OxyContin, Drug Identification Chart of “Abused Pharmaceutical Substances” by the National Association of Drug Diversion Investigators (NADDI), Press Release 10/13/03, entitled “Tamper-Resistant Prescription Pads Offered to Michigan Physicians to Help Reduce Prescription Drug Diversion,” Visual Aid:	PDD1501128421

			“There Can be Life with Relief,” Site Navigation for OxyContin Information in “Newsroom” of Purdue’s Corporate Website, wholesaler pricing schedule	
OxyContin	11/24/2003	To FDA	Letter from Purdue on the promotional activities of Oxytrex and Remoxy	Bates Unavailable
OxyContin	11/25/2003	From FDA	<p>FDA letter to Purdue following-up on the 1/17/2003 Warning Letter.</p> <p>“At this juncture, DDMAC requests that Purdue confirm in writing that the aforementioned corrective advertisement was published according to your stated plan.”</p> <p>DDMAC requested a list of all current promotional materials for OxyContin</p> <p>“Lastly, DDMAC requests that Purdue provide the following information:</p> <ul style="list-style-type: none"> • All websites funded in whole or in part by Purdue relating to pain management and treatment, including but not limited to, websites supported through grants to third parties. • Describe Purdue’s role in the content selection, development, review or maintenance of these websites.” 	PPLPC009000104941
OxyContin	12/3/2003	From FDA	From FDA in response to Purdue’s 11/4/03 letter on the promotional activities of Janssen.	PDD8003187301
OxyContin	12/3/2003	To FDA	Submission of Journal Ad: There Can Be Life with Relief” (Fishing) and wholesaler pricing schedule for review	PDD8013033520
OxyContin	12/4/2003	From FDA	Letter from the FDA in response to Purdue’s letter on the promotional activities of Oxytrex and Remoxy.	PDD8003186991
OxyContin	12/9/2003	To FDA	Submission of the following promotional items for review: Purdue’s Response to Recent Questions from the Orlando Sentinel Newspaper Regarding OxyContin, Purdue’s Opinion-Editorial Piece Appearing in the Connecticut Post Newspaper in Response to a 11/5/03 Piece by Kay Kelley-Moretti Regarding OxyContin, American Pain Society’s “Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain,” Fifth Edition, Q12H Flashcard (Fisherman), wholesaler pricing schedule	PDD8013033759
OxyContin	12/15/2003	To FDA	Contents Not Reported	Bates Unavailable
OxyContin	12/17/2003	To FDA	Submission of the following promotional	PDD8013034502

			<p>items for review: Purdue's Op-Ed Article to Appear in York, Pennsylvania's "Daily Record" Newspaper, entitled: "Misinformation about Prescription Drugs Just as Harmful," Purdue's Presentation Made to Staff of the "Roanoke Times" (Virginia) Newspaper on 10/3/03 Regarding OxyContin Abuse, Oregon Preferred Drug List: Explanation of the Exception Process from the HB3624 [that was Signed by the Governor on 9/24/03], Purdue's Public Affairs Dept. Informational Text, entitled: "Common Errors in Media Reporting about OxyContin Tablets," Purdue's Public Affairs Dept. Informational Text dated 10/14/03, entitled: "Statement Refuting Suggestion that Use of OxyContin Tablets is Connected with Hearing Loss," Purdue's Public Affairs Dept. Revised Informational Text, entitled: "Common Errors in Media Reporting about OxyContin Tablets," Notification of an Arizona Upcoming Policy Change to Mercy Care Plan AHCCCS Providers: Provide the Formulary Notification Letter and a Contact Sheet for Comments Back to AHCCCS, Press Release 12/1/03, entitled: "65-0 OxyContin Cases Against Purdue Pharma Dismissed at Record Rate," OxyContin Ceiling Reference Card (Fisherman), wholesaler pricing schedule</p>	
OxyContin	1/27/2004	To FDA	<p>Submission of the following promotional items for review: Purdue's Public Affairs Dept. Informational Text Prepared in Response to Allegations Made in "Pain Killer" Book Authored by Barry Meier, Washington State's Memo Issued on 10/6/03 Regarding Updates to that State's Prescription Drug Program, Purdue's 11/6/03 Informational Text Prepared in Response to Questions Posed by Reporter Barry Meier on 11/4/03, Purdue's Letter to Reporter Doris Bloodworth of the Orlando (Florida) Sentinel Newspaper in Response to a Nov. 2003 Press Release by the "Relatives Against Purdue Pharma," Purdue's 1/6/04 Letter to "Managed Care Partner" Regarding Recent OxyContin Patent Issue, Purdue's 1/8/04 Letter to "Managed Care Partner" Regarding Recent OxyContin Patent Issue, including a 1/7/04 Press Release entitled "Statement Regarding U.S. District Court Ruling on Purdue Patents for OxyContin</p>	PDD8013035510

			Tablets,” Purdue’s 1/8/04 Letter to “Trade Partner” Regarding Recent OxyContin Patent Issue, including a 1/7/04 Press Release Entitled “Statement Regarding U.S. District Court Ruling on Purdue Patents for OxyContin Tablets,” Convention Panel (Fisherman) for Regional Display Booth, 2004-2005 Calendar (Fisherman), wholesaler pricing schedule	
OxyContin	2/12/2004	From FDA	<p>FDA’s response to PPLP’s 10/29/03 submission.</p> <p>OxyContin 10/20 mg Visual Aid</p> <ul style="list-style-type: none"> “...you present the claim ‘OxyContin is not for everyone’ along with several bullets describing situations where OxyContin use is inappropriate. This presentation is misleading because you fail to present important risk information that describes patient populations where OxyContn use is contraindicated...” <p>Osteoarthritis – Pain 1</p> <ul style="list-style-type: none"> “You present the claim ‘Persistent pain due to osteoarthritis.’ This claim is misleading because it implies that all patients with persistent pain due to osteoarthritis are appropriate candidates for OxyContin when such is not the case...” “You present claims describing the change in the patient’s...drug regimen of hydrocodone/acetaminophen 5/500 mg 2 tablets q6h to OxyContin 20 mg q12h. This presentation is misleading because it suggests a higher dosage of OxyContin than is recommended (i.e. 10 mg q12h) based on the conversion guidelines put forth in the Dosage and Administration section of the PI.” “Your proposed case study presents the history of a patient who was unable to tolerate treatment with an NSAID and was started on OxyContin because the patient’s ‘pain ratings decreased but patient complained of inadequate duration of 	PURCHI-000764097

analgesia' with two hydrocodone/acetaminophen (5/500 mg) tablets every 6 hours. The patient was started on OxyContin 20 mg every 12 hours. A 0-10 pain scale is presented and labeled 'Initial pain scale ratings' and is marked with an arrow extending from 8-10. Another 0-10 pain scale labeled 'Pain ratings at follow-up' is marked with an arrow extending from 0-3. This presentation is misleading because it implies that OxyContin is more effective than hydrocodone/acetaminophen when such has not been demonstrated by substantial evidence. Furthermore, this presentation is misleading because it overstates OxyContin's effectiveness, thereby implying all patients will experience this level of pain relief when such has not been demonstrated."

- "You describe the patient in this case study as 'G.L., 52-year-old male, truck driver.' This presentation is misleading because you omit important risk information, thereby minimizing the risks associated with OxyContin. Specifically, you fail to present information from the PI that states 'OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).' DDMAC suggests including this material fact prominently with this presentation to avoid a misleading message."

Osteoarthritis – Pain 2

- "You present the claim 'Patient has difficulty performing daily activities, such as shopping and housecleaning' under the header 'Clinical history and presentation' followed by the claim 'Patient activity level improved, is able to walk at the mall with her husband' under header 'Outcome.' This presentation is misleading

			<p>because it implies that OxyContin improves patients' abilities to perform daily activities when such is not supported by substantial evidence."</p> <p>Rheumatoid Arthritis Pain</p> <ul style="list-style-type: none"> • "You present a profile entitled 'Persistent Pain Due to Rheumatoid Arthritis' along with two visuals entitled 'Initial pain scale ratings' and 'Pain ratings at follow-up.' This patient profile is misleading because it implies that the efficacy of OxyContin has been established in a Rheumatoid Arthritis Pain Model when such is not the case." • Proposed case study is misleading "because it implies that OxyContin decreased the patient's level of pain from 7-8 to 0-2, thereby implying that OxyContin is more effective than oxycodone/acetaminophen when such has not been demonstrated by substantial evidence. Furthermore, this presentation is misleading because it overstates OxyContin's effectiveness, thereby implying that all patients will experience this level of pain relief when such has not been demonstrated." 	
OxyContin	2/26/2004	To FDA	<p>Submission of the following promotional items for review: Updated Purdue Public Affairs' Statement Regarding U.S. District Court Ruling on Purdue Patents for OxyContin, Revised Purdue Public Affairs' Statement Regarding U.S. District Court Ruling on Purdue Patents for OxyContin, Purdue's Response (entitled, "Misplaced Blame will not Solve Drug Abuse Problem") to a 12/14/03 Editorial in the Lexington Herald-Leader Newspaper Regarding Purdue's Role in Kentucky's Substance Abuse Problems, Purdue Public Affairs' Informational Text 1/22/04 entitled "Purdue Pharma Comments of GAO Report on OxyContin Abuse and Diversion," Purdue's Opinion-Editorial Article (entitled "Don't Forget the Patients") Appearing in the Orlando Sentinel Newspaper Regarding Florida's Prescription Drug Abuse Problem,</p>	PDD8013036456

			Purdue Public Affairs' Informational Text 1/29/04 entitled "Purdue Pharma Statement on Attorney General Blumenthal's Citizen Petition to the U.S. Food and Drug Administration," Purdue Letter 1/29/04 to Dennis FitzSimons, head of the Tribune Company in Chicago, IL regarding Recent Articles in the Orlando Sentinel Newspaper about OxyContin, Purdue Letter 2/2/04 to Dennis FitzSimons regarding a 2/1/04 Article in the Orlando Sentinel Newspaper entitled, "OxyContin Maker Says Patient is not Credible; Ex-Cop Profiled in Articles had Drug-Related Conviction," Press Release 1/12/04 entitled "Purdue Pharma Files Notice of Appeal in the Endo Patent Case; Commits to Expedited Process," Revised OxyContin q12h Flashcard, wholesaler pricing schedule	
OxyContin	3/10/2004	To FDA	Submission of the following promotional items for review: Corporate Overview Presentation, Revisions to Purdue.Pharma.com Website, wholesaler pricing schedule	PDD8013037511
OxyContin	3/16/2004	To FDA	Submission of the following promotional items for review: Purdue Informational Text: A Timeline of Purdue Events Surrounding Prescription Drug Abuse, Purdue Informational Text entitled "Purdue v. Endo Patent Decision," Purdue's 2/13/04 (by Howard Udell) to David Bralow, Attorney for the Orlando Sentinel Newspaper, about OxyContin Articles Appearing in that Periodical from 10/19/03 through 10/23/03, Purdue's 2/19/04 Letter (by Howard Udell) to Gregg Thomas of Holland and Knight Regarding OxyContin Articles Appearing in the Orlando Sentinel Newspaper	PDD8013037714
OxyContin	4/16/2004	To FDA	Submission of the following promotional items for review: OxyContin 80 mg Tablets Retail Sell Sheet, wholesaler pricing schedule	PDD8013038639
OxyContin	4/21/2004	To FDA	Submission of the following promotional items for review: 2004 Pain Management Prescribing Guide, Purdue Files, Serves Appeal Brief in Endo Case, OxyContin Letter regarding Rebate, wholesaler pricing schedule	PDD8013038783
OxyContin	5/26/2004	To FDA	Submission of the following promotional items for review: Cost Reduction Statement, Package Insert, wholesaler pricing schedule	PDD1501128666

OxyContin	6/7/2004	To FDA	Submission of the following promotional items for review: Response to Allegations and Misconceptions about Purdue's Marketing of OxyContin Tablets, Purdue Pharma Statement in Response to "FDA Enforcement Actions Against False and Misleading Prescription Drug Advertisements Declined in 2003," Package Insert, wholesaler pricing schedule	PDD8003229320
OxyContin	7/12/2004	To FDA	Submission of the following promotional items for review: 2004 Pain Management Prescribing Guide, Package Insert, wholesaler pricing schedule	PDD8013041845
OxyContin	7/21/2004	To FDA	Submission of the following promotional items for review: OxyContin Rebate Retail Sell Sheet, 3-2 Letter, Package Insert, wholesaler pricing schedule	PDD8013042022
OxyContin	8/13/2004	To FDA	Submission of the following promotional items for review: Orlando Sentinel Correction Website Newsroom Addition OM – Public Affairs Informational Text, Package Insert, wholesaler pricing schedule	PDD8013042245
OxyContin	8/20/2004	To FDA	<p>PPLP submits two revised draft case studies for review and comment prior to dissemination by the sales force.</p> <ul style="list-style-type: none"> In the 2/12/04 letter the FDA noted misleading dosage and administration claims in the "Case Study 1 in Osteoarthritis." PPLP responded that the reference case study was provided with the 10/29/03 submission. Dr. Smith provided subsequent additional information attached to this response. 	PURCHI-000764097
OxyContin	8/23/2004	To FDA	Submission of the following promotional items for review: Artwork, wholesaler pricing schedule, Package Insert	PDD8013042377
OxyContin	8/27/2004	To FDA	Submission of the following promotional items for review: Op/Ed for Orlando Sentinel, Drug Abuse: Update of Federal Data, Package Insert, wholesaler pricing schedule	PDD8003254460
OxyContin	9/7/2004	To FDA	Submission of the following promotional items for review: Orlando Sentinel Retraction, Package Insert, wholesaler pricing	PDD8013042714
OxyContin	9/23/2004	To FDA	Submission of the following promotional items for review: OxyContin Reprint Carrier, Sticky Pads (Post-It Notes), Fat Pens #2 –	PDD1501128775

			Only OxyContin Printed on Pen, Click Pens – Only OxyContin Printed on Pen, DEA and Pain Experts Joint Statement Ad FAQs, Package Insert, wholesaler pricing schedule	
OxyContin	9/28/2004	To FDA	Submission of the following promotional items for review: OxyContin Pull-Up Window Shade Banner Stand, Package Insert, wholesaler pricing schedule	PDD8003255048
OxyContin	11/8/2004	To FDA	Submission of the following promotional items for review: Revised OxyContin A-Sized 1 page fishing Ad, Revised OxyContin A-Sized 2 page spread ad, Revised OxyContin Digest Sized 1 page, Revised OxyContin Tabloid-Sized 1 page	PDD8013044062
OxyContin MS Contin	11/10/2004	To FDA	Submission of the following promotional items for review: 2005 PDR (Rx Products), Package Insert, wholesaler pricing schedule	PDD8013044137
OxyContin	11/11/2004	To FDA	Submission of the following promotional items for review: www.purduepharma.com Prescription Medicines, Package Insert, Current Pricing Letter	PDD8013044252
OxyContin	11/15/2004	To FDA	Submission of the following promotional items for review: Abuse and Diversion “Orlando Sentinel” Correction Letter to Thought Leaders, Package Insert, wholesaler pricing schedule	PDD8013044625
OxyContin	11/24/2004	To FDA	Submission of the following promotional items for review: RFID Press Release, Package Insert, wholesaler pricing schedule	PDD8003258226
OxyContin	12/9/2004	To FDA	Submission of the following promotional items for review: Michael Friedman’s Speech (and slides) for Pharmaceutical Regulatory and Compliance Congress, Package Insert, wholesaler pricing schedule	PDD8013046395
OxyContin	12/16/2004	To FDA	Submission of the following promotional items for review: Video Footage of RFID B-Roll, Presentation on the RADARS System, Package Insert, wholesaler pricing schedule	PDD8013046334
OxyContin	12/18/2004	To FDA	Submission of the following promotional items for review: A Public Relations Speech entitled “Purdue Pharma’s Response to the OxyContin Controversy” for Conference Board Council on Corporate Communications Strategy, Package Insert, wholesaler pricing schedule	PDD8013047263
OxyContin	12/20/2004	To FDA	Submission of the following promotional items for review: New Managed Care Long-Acting Opioid Economic Model, Package Insert, Pricing Letter	PDD8003258830
OxyContin	1/13/2005	To FDA	Submission of the following promotional items for review: Indiana Circuit Court	PDD8013046865

			Denies Class Certification in OxyContin Litigation, Package Insert, wholesaler pricing schedule	
OxyContin	2/1/2005	To FDA	Submission of the following promotional items for review: Communication to Virginia Field Sales Representatives Re: Virginia Medicaid Long Acting Opioid Step Therapy Policy set for implementation on 1/1/05 and Virginia Dept., Package Insert, wholesaler pricing	PDD8013047024
OxyContin	2/16/2005	To FDA	Submission of the following promotional items for review: New York Class Action Press Release, Package Insert, wholesaler pricing schedule	PDD8013047205
OxyContin	2/18/2005	To FDA	Submission of the following promotional items for review: Public Relations Speech entitled, "Purdue Pharma's Response to the OxyContin Controversy" for Conference Board Council on Corporate Communications Strategy, Package Insert, wholesaler pricing schedule	PDD8013047263
OxyContin	3/2/2005	To FDA	Submission of the following promotional items for review: OxyContin: Vermont Price Disclosure Short Form and Long Form, Package Insert, wholesaler pricing schedule	PURCHI-000782639
OxyContin	3/10/2005	To FDA	Submission of the following promotional items for review: Department of Veterans Affairs Authorized Federal Supply Schedule Pricelist, Package Insert, wholesaler pricing schedule	PDD8013047566
OxyContin	3/11/2005	To FDA	Submission of the following promotional items for review: Revised OxyContin Journal Ad, Package Insert, wholesaler pricing schedule	PDD8013047695
OxyContin MS Contin	3/16/2005	To FDA	Submission of the following promotional items for review: RADARS presentation for KASPER in KY on 3/30/05, Package Insert, wholesaler pricing schedule	PDD8013047738
OxyContin	3/18/2005	To FDA	Submission of the following promotional items for review: OxyContin Logo Exhibit Panel, Revised Montage Panel, Package Insert, wholesaler pricing schedule	PDD8013047821
OxyContin	4/11/2005	To FDA	Submission of the following promotional items for review: OxyContin Montage Panel, Litigation Dismissals and Withdrawals Grow to 306, Screensaver with OxyContin Logo, Box Warning, and Package Insert, Package Insert, wholesaler pricing schedule	PDD8013048270
OxyContin	4/14/2005	To FDA	Submission of the following promotional items for review: Press Release – FBI – LEEDA Recognizes Purdue Pharma for	PDD8013048626

			Innovative Contributions to Law Enforcement, Package Insert, wholesaler pricing schedule	
OxyContin	4/21/2005	To FDA	PPLP submitted two draft promotional visual aids for the 10 mg tablet and 20 mg tablet for review and comments.	PURCHI-000783763
OxyContin MS Contin	4/26/2005	To FDA	Submission of the following promotional items for review: Updated Distributor/Mass Merchandiser, Medical/Surgical Dealer, Wholesaler, Mail Order Pharmacy, Closed Provider Pharmacy Chains, Food Chains and Food Wholesaler and Hospital and Govt. Hospital Pricing Schedules, Package Insert	PDD8013049160
OxyContin	5/11/2005	To FDA	Letter from Purdue to the FDA advising them of the submission of the Conversion Guide which was not submitted at the time of first issue and was since discontinued. Submission of the following promotional items for review: Revised OxyContin Conversion Reference Chart, Package Insert, wholesaler pricing schedule	PDD8013049511
OxyContin	5/13/2005	To FDA	Submission of the following promotional items for review: 12/1/04 Price Increase Letter, Terms, and Pricing Schedules for Wholesalers, Chain, Hospitals, and Government, Package Insert	PDD8013049568
OxyContinMS Contin	5/19/2005	To FDA	Submission of the following promotional items for review: Price Increase Letter, Terms, and Pricing Schedules for Wholesalers/Chains, Hospitals/Govt Hospitals, Package Insert	PDD8013049990
OxyContin	5/23/2005	From FDA	FDA response to PPLP's 8/20/04 request for review and comments. Case Study 1 in Osteoarthritis <ul style="list-style-type: none"> FDA referred to their comments from 2/12/04 on the misleading omission of material fact. 	PURCHI-000784847
OxyContin	5/23/2005	From FDA	FDA response to PPLP's 4/21/05 request for review and comments. Visual Aids for 10 mg & 20 mg <ul style="list-style-type: none"> "The back cover of the proposed visual aid includes risk information from the Boxed Warning, Contraindications, and Adverse Reactions sections of the OxyContin PI under the header 'Important safety information.' This presentation is misleading because it 	PURCHI-000784844

			<p>minimizes risks associated with OxyContin use and implies that the risk information under this header constitutes all of the safety information associated with the use of OxyContin.</p> <ul style="list-style-type: none"> “On the back cover of the proposed visual aid is a graph titled, ‘A Guide to Titration of OxyContin Tablets.’ This presentation is misleading because it lacks important contextual information. According to the Dosage and Administration section of the PI (in part), ‘Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h.’ We recommend you include this important contextual information.” 	
OxyContin MS Contin	5/26/2005	To FDA	Submission of the following promotional items for review: PowerPoint Presentation for Training Healthcare Professionals entitled, “Lawful Prescribing and Prevention of Diversion,” Package Insert, wholesaler pricing schedule	PDD8013050128
OxyContin	5/31/2005	To FDA	Submission of the following promotional items for review: Testimony to the Massachusetts Joint Committee on Mental Health and Substance Abuse Scheduled on May 2, 2005, Medicaid 80 mg pricing information, Package Insert	PDD8013050244
OxyContin	6/9/2005	To FDA	Submission of the following promotional items for review: OxyContin Vermont Information for Prescribers Short Form – June, 2005, Package Insert, wholesaler pricing schedule	PDD8013050373
OxyContin MS Contin	6/13/2005	To FDA	Submission of the following promotional items for review: Update Wholesaler/Chain, Hospital/Government Hospital, Medical Surgical Dealer, Distributor/Veterinary Distributor, Package Insert	PDD8013050456
OxyContin	6/15/2005	To FDA	Submission of the following promotional items for review: Information for Vermont Prescribers OxyContin Long Form, OxyContin 80 mg DAW 3-Wave Mailing #1 with envelope, Package Insert, wholesaler	PURCHI-000791806

			pricing schedule	
OxyContin	6/16/2005	To FDA	Submission of the following promotional items for review: OxyContin 10 mg Dose Related Visual Aid, OxyContin 10 & 20 mg case study 2OA, Package Insert, wholesaler pricing schedule	PDD8013050705
OxyContin	6/20/2005	To FDA	Submission of the following promotional items for review: OxyContin DAW Handout for Field Force Distribution, Revised Statement of Purdue Pharma in Response to an Adverse Decision by the Federal Circuit, Package Insert, wholesaler pricing schedule	PDD8013050784
OxyContin	9/14/2005	To FDA	Submission of the following promotional items for review: Small but Important Changes to www.purduepharma.com to Reflect Recent Company Developments, The Decision in Purdue v. Endo, OxyContin DAW Journal Ad, Vermont Pricing Sheet for Q3 – OxyContin, Titration Guide, Press Release – Purdue and Labopharm Enter U.S. Licensing Distribution Agreement for Once-Daily Tramadol	PDD8013051684
OxyContin	10/28/2005	To FDA	Submission of the following promotional items for review: Coupon Book, Massachusetts OxyContin Commission Testimony of Alan Must, Massachusetts OxyContin Commission Testimony of Dr. J. David Haddox, Review of Purdue Testimony for Congressional Hearing 9/13, PowerPoint Slide Presentation: “Abuse and Diversion of Prescription Drugs” – LELE Version	PURCHI-000795183
OxyContin	12/14/2005	To FDA	Submission of the following promotional items for review: 2005 Pain Prescribing Guide, Revised Vermont Forms – OxyContin, New OxyContin Unit Dose Packaging (Bar-coded) National Accounts Information Sheet, New OxyContin Unit Dose Packaging Institutional Sales & Planning Information Sheet, Watson Announcement 10/18/05 – Purdue Appoints Watson Pharmaceuticals Exclusive Distributor of Authorized Generic Version of OxyContin Tablets	PURCHI-000800570
OxyContin	1/19/2006	To FDA	Submission of the following promotional items for review: Update Wholesaler/Chain, Hospital/Government Pricing Schedules to include the new OxyContin 20 count Unit Does, Oxycodone Hydrochloride Journal Ad from Watson Pharmaceuticals, OxyContin Tablets Bar-Coded Unit Dose 20 Count Information Sheet/Visual Aid, OxyContin	PURCHI-000800982

			Medi-Cal Information Sheet	
OxyContin	2/27/2006	To FDA	Submission of the following promotional items for review: Update Wholesaler/Chain Hospital, Hospital/Govt Hospital, Puerto Rico Wholesaler, Puerto Rico Chain pricing schedules, Standard "go-by" Letter Used by Law Enforcement Agencies to Request OxyContin Placebo Tablets	PDD8013052197
OxyContin	3/23/2006	To FDA	Submission of the following promotional items for review: Drug Identification Cards of Prescription Opioid Analgesics and Stimulants Marketed in Canada, Sample Representation of Watson Pharma's Letters to Pharmacies Offering Prices and Incentives for Oxycodone, Update OxyContin Pricing Disclosure Information for VT Prescribers, BNA Article Reprint for Account Executives, Oxycodone HCI Controlled Release Tablet Convention, Statement of Purdue Pharma Regarding Endo Patent Decision	PDD8013052344
OxyContin	6/8/2006	To FDA	Submission of the following promotional items for review: OxyContin Updated Pricing Disclosure Information for Vermont Prescribers, Oxycodone ER Marketplace Fact Sheet	PDD8013053084
OxyContin	8/16/2006	To FDA	Submission of the following promotional items for review: Statement of Purdue Pharma in Response to the Final Report of the Massachusetts, Watson Pharmaceuticals One Page Convention Panel for Oxycodone Controlled Release Tablets and Morphine Controlled Release Tablets, OxyContin \$20 Discount Program: Carton Containing Patient Info Sheets with Prescription Discount Card and SENOKOT Rebate	PDD8013053588
OxyContin	8/18/2006	To FDA	Submission of the following promotional items for review: OxyContin \$50 Discount Program: Carton containing Patient Info Sheets with Prescription Discount Card and SENOKOT Rebate	PDD8013053608
OxyContin	9/22/2006	To FDA	Submission of the following promotional items for review: Revised Vermont Pricing Disclosure Forms - OxyContin	PDD8013053893
OxyContin	10/20/2006	To FDA	Submission of the following promotional items for review: OxyContin Delivery System Visual Aid, Purdue Pharma Announces Resolution of OxyContin Patent Lawsuit with Endo Pharmaceuticals, Purdue Pharma Announces Agreement to End OxyContin Patent Lawsuit with Teva	PDD8013053981

			Pharmaceuticals	
OxyContin	11/10/2006	To FDA	Submission of the following promotional items for review: Purdue Pharma LP Announces Signing of Consent Judgment Ending OxyContin Tablets Patent Lawsuit with Teva Pharmaceuticals	PDD8013264785
OxyContin MS Contin	2/16/2007	To FDA	Submission of the following promotional items for review: Department of Veterans Affairs Authorized Federal Supply Schedule Pricelist – OxyContin, MS Contin, Package Insert	PDD8013054611
OxyContin	3/20/2007	To FDA	Submission of the following promotional items for review: Response to Questions on Availability of OxyContin Tablets and its Generic Formulations, OxyContin \$50 Program, Updated OxyContin VT Pricing Disclosure Sheets, Summary/Update on OxyContin Tablets Patent Case/Market Situation	PURCHI-000816773
OxyContin	4/4/2007	To FDA	Submission of the following promotional items for review: Price Increase for RX Products and to delete discontinued products (OTC) for Wholesalers – OxyContin, MS Contin, Price Increase for RX Products and to delete discontinued products (OTC) for Puerto Rico Chains – OxyContin, MS Contin, Price Increase for RX Products and to delete discontinued products (OTC) for Wholesalers/Chains – OxyContin, MS Contin, Price Increase for RX Products and to delete discontinued products (OTC) for Hospitals/Government Hospitals – OxyContin, MS Contin, Package Insert for MS Contin	PDD8013054691
OxyContin	5/14/2007	To FDA	Submission of the following promotional items for review: 2007 Aetna Preferred Drug, OxyContin PI Letter to the Wholesalers, Response to questions on availability of OxyContin Tablets and its generic formulations, OxyContin \$50 Patient Savings Program Pharmacist Instructions, OxyContin Info Letter NAMS PDF Print Used by NAMS Only, OxyContin Acrocontin Delivery System Visual Aid, ACP 2007 Beaming Satation Logo and Content,	PDD8013055137
OxyContin	6/13/2007	To FDA	Submission of the following promotional items for review: OxyContin Net Cost Model, Key Initiatives to Combat Prescription Drug Diversion & Abuse, Wire Service: Terms of Agreement with	PDD8013055846

			Government, Key Initiatives to Ensure Appropriate Product Promo & Prescribing, Information for VT Prescribers – OxyContin, OxyContin NAM Info Letter, Market Situation Summary Sheet, OxyContin REP Info Letter PDF/Print use by Field Force	
OxyContin	8/13/2007	To FDA	Contents Not Reported	Bates Unavailable
OxyContin	8/31/2007	To FDA	Submission of the following promotional items for review: Letter to Advise Both Direct and Indirect of Correct Company Name of Our Products, Customized Letter to Accompany APS Booklet (PAP058) request from University of Maryland School of Pharmacy, PAP Letter to Accompany PAP058-APS “Principles of Analgesic Use in the Treatment of Cancer Pain” 5 th Edition, Announcement Letter to Hospice Regarding Update with Patient Letter, Rebate Summary and Exhibits A-C, OxyContin Convention Panels – Nice Lady Panel and Box Warning Panel – Annual Review of Panels, OxyContin Convention Panels – Blues Guy Panel and Box Warning Panel – Annual Review of Panels, Statement of Purdue Pharma regarding July 31 Hearing of the Senate Judiciary Committee, Statement by Howard Shapiro, the Purdue’s corporate legal counsel in the WDVA settlement and a document summarizing Mr. Shapiro’s longer statement, OxyContin REP Info Letter PDF / Print use by Field Force, Purdue Pharma LP Announces End of OxyContin Patent Lawsuit with IMPAX Laboratories, US Government Response – Main Document, Statement of Purdue Pharma Regarding July 20 Proceedings in the US District Court for the Western District of VA, Hospice Patient Letter, Video Clips – Obtaining RX’s by Fraud and Deceit	PDD8013274768
OxyContin	10/4/2007	To FDA	Submission of the following promotional items for review: PAP Medical Letter to Accompany Dissemination Item 00RO48, Vermont Pricing Disclosure Forms, OxyContin RFID Letter to the Trade Accounts, Medical Letter to Accompany Dissemination of PAP058, OxyContin ShopRite Patient Pad/Info Sheet, OxyContin Kmart Info Sheet/Patient Pad, OxyContin DIK Info Sheet/Patient Pad, Revision OxyContin and Its Generic Pads for Pharmacist Distribution to Patients,	PDD8013274975

			OxyContin Physician Info Sheet/Pad	
OxyContin	11/1/2007	From FDA	DDMAC reviewed PPLP's proposed press release submitted on 8/13/2007 and offered no objections.	PDD8013057205
OxyContin	11/13/2007	To FDA	Submission of the following promotional items for review: Drogueria Castillo (Spanish) Info Sheet/Pad, Spanish Info Sheet/Pad, Medical Letter to Accompany the reorder of Item PAP058-APSB, Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 5 th Edition, AAFP 2007 PDA Download Station PAP and Oxy Content, Purdue Statement – Kentucky Litigation 10/4/07, Revised Vermont Pricing Disclosure – OxyContin, OxyContin Health Wise Info Sheet/Patient Pad	PDD8013299989
OxyContin	1/8/2008	To FDA	Contents Not Reports	Bates Unavailable
OxyContin	1/11/2008	To FDA	Submission of the following promotional items for review: \$50 Patient Savings Card Sticker, \$50 Patient Savings Card Program Extension Flyer, Dispense As Written (DAW) Visual Aid, Vermont Pricing Disclosure Forms, Letter to PBM's and HMOs Announcing the Introduction of OxyContin Intermediate Strengths, Cover Letter for Contract Amendment, Pain 2 Case Study, Intermediate Dosage WAC Sell Sheet	PDD8013057129
OxyContin	2/14/2008	To FDA	Submission of the following promotional items for review: Crime Stoppers Release – Corryville Robbery – Cincinnati, OH, Crime Stoppers Release – Louisa, KY, Federal Court Affirms Enforceability of OxyContin Patents, Statement of Purdue Regarding Endo Patent Decision, Crime Stoppers Release – Scottsdale, AZ, Update Wholesaler/Chain to reflect the introduction of three new strengths of OxyContin and five percent increase on existing OxyContin SKUs, Update Hospital/Govt Hospital to reflect the introduction of three new strengths of OxyContin and five percent increase on existing OxyContin SKUs, Update Puerto Rico to reflect the introduction of three new strengths of OxyContin and five percent increase on existing OxyContin SKUs, Crime Stoppers Release – Kingsport, TN, Crime Stoppers Release, Southern NJ Crime Commission, Crime Stoppers Release – Cincinnati, OH, Crime Stoppers Release – Springfield and Anderson Township – Greater Cincinnati,	PDD8013311954

			Patient Assistance Program Brochure, Statement of Purdue Pharma in Response to the Decision Confirming the Enforceability of its OxyContin Patent, Letter to PBMs, HMOs, and GPOs announcing the introduction of OxyContin Intermediate Strengths, Cover Letter for Contract Amendment – Revision, Intermediate Dosage Wholesale Sell Sheet, Intermediate Dosage WAC Sell Sheet, Notification – Patent Decision, Market Summary Sheet – OxyContin, PowerPoint Presentation by Mike Celentano to California Board of Pharmacy Meeting on January 23, 2008, Update OxyContin MSDSs and Add New Ones for Intermediate Doses, Gradient Pens (To be Distributed with Current PI OT01343 A dated 11/5/07), Hospice Rebate Program Mailing Announcing Addition to OxyContin 15mg, 30mg, 60mg Tablets and Increased Rebates on Existing OxyContin Strengths (10mg, 20mg and 80mg tablets), New OxyContin Journal Ad	
OxyContin	4/1/2008	To FDA	Submission of the following promotional items for review: Product Pictures for Red Book, Federal Supply Schedule Purdue Pharma LA – Revision, Article of Pathways, American Society for Pain Management Nursing Newsletter, Association National Oxynewtab e-letter – Pamela Bennett, Review of Photo and Caption for New Dosage Strengths, Press Release announcing Availability of New Dosage Strengths 031008, Matt K Story – Impaired Pharmacist DVD Label, e-M.D./Alert,	PDD8013057256
OxyContin	4/29/2008	To FDA	Submission of the following promotional items for review: New Strengths Conversion Titration Guide, Main Visual Aid – OxyContin, Crime Stoppers Release – St. Petersburg, FL, Flashcard – New Strengths Revised, Crime Stoppers Release – Bradenton, FL, Crime Stoppers Release – Orlando, FL, \$50 Patient Savings Card, Updated Boxed Warning – Statement of Purdue Pharma regarding July 31 Hearing of the Senate Judiciary Committee, Purdue Statement on AG Blumenthal’s Compliant File Against the US Food and Drug Administration, OxyContin Header Convention Panel	PDD8013311814
OxyContin	6/2/2008	To FDA	Submission of the following promotional	PDD8013311692

			<p>items for review: TMS Cycle 2 Follow-up Letter #6 – Scenario 2 Script – Packet A, TMS Cycle 2 Follow-up Letter #5 – Scenario 2 Script – Packet A+C, TMS Cycle 2 Follow-up Letter #4 – Scenario 1 Script – Packet D, TMS Cycle 2 Follow-up Letter #8 – Scenario 2 Script – Packet D, TMS Cycle 2 Follow-up Letter #7 – Scenario 2 Script – Packet C, TMS Cycle 2 Follow-up Letter #3 – Scenario 1 Script – Packet C, TMS Cycle 2 Follow-up Letter #1 – Scenario 1 Script – Packet A+C, TMS Cycle 2 Follow-up Letter #2 – Scenario 1 Script – Packet A, Crime Stoppers Release – Altamonte Springs (Orlando) Robbery, Crime Stoppers Release – Volusia County, FL Robbery, Crime Stoppers Release – Jacksonville, FL Pharmacy Robbery, Crime Stoppers Release – Lafayette, LA, OxyContin Brookshire Brothers Info Sheet/Patient Pad, TMS OxyContin Script Cycle 2-3 Scenarios, OxyContin GNP Info Sheet/Patient Pad, OxyContin Shopko Info Sheet/Patient Pad, Rochester Drug Cooperative Info Sheet/Patient Pad, A Case Study on Drugs Containing a Controlled Substance, Duane Reade Info Sheet/Patient Pad, Flashcard with 15 and 30 mg Oxycodone IR Alert, Rep Info Sheet/Patient Pad, \$60 Patient Savings Card Pad, FDA Advisory Committee Statement, Updated Boxed Warning Statement of Purdue Pharma Regarding July 20 Proceedings in US District Court, Albertson's Supervalu Info Sheet/Patient Pad</p>	
OxyContin	7/2/2008	To FDA	<p>Submission of the following promotional items for review: Revised OxyContin Conversion/Titration Guide – All Dosages, Low-Dose Flashcard, \$60 Savings Card Pharmacist Instruction (Info) Sheet, Vermont Pricing Disclosure Forms – OxyContin Tablets, Generic (MD) Info Sheet/Patient Pad, Annual Review / Update (Boxed Warning) – Purdue Pharma LP Announces End of OxyContin Patent Lawsuit, Delivery System Visual Aid, New OxyContin Conversion/Titration Guide Low Dose (10-40 mg), Crime Stoppers Release – Toledo, OH Two Robberies</p>	PDD8013311894
OxyContin	8/5/2008	To FDA	<p>Submission of the following promotional items for review: Convention Panel – Flexibility Through Seven Tablet Strengths,</p>	PDD8013312258

			Revised "SALES AID – Flexibility with OxyContin Tablets," Convention Panel Flexibility with OxyContin Tablets 10mg – 80mg, Crime Stoppers Release – Everett, WA Pharmacy Robbery, Crime Stoppers Release – Salt Lake City, UT (West Jordan) Pharmacy Robbery 7/3/08 REVISED, Crime Stoppers Release – Jacksonville, FL, Crime Stoppers Release – Fort Myers, FL Robbery, Crime Stoppers Release – Toledo and Tiffin Three Robberies, Crime Stoppers Release – Anderson, IN Pharmacy Robbery, Crime Stoppers Release – Salt Lake City, UT (West Jordan) Pharmacy Robbery, Crime Stoppers Release – Auburn, MA Pharmacy Robbery, RFID UHFGen2 Healthcare Packaging PowerPoint, Annual Review – Updated Box Warning – Statement by Howard Shapiro, Purdue's Corporate Legal Counsel, Annual Review – Updated Box Warning – Statement of Purdue Pharma regarding 7/31/07 Hearing of State Judiciary Committee, Scenario 1 Script – TMS Script for Call Cycle 3, TMS Cycle Follow-Up Letter B.3.3.- Scenario 3 Script, TMS Cycle Follow-Up Letter A.3.1.- Scenario 1 Script, Scenario 2 Script – TMS Script for Call Cycle 3, Scenario 2 Scripts – TMS Script for Call Cycle 3, Scenario 1 Script – TMS Script for Call Cycle 3, Corporate Security HCP Presentation, Revised OxyContin Conversion/Titration Guide-Low Dose (10-40mg), Revised OxyContin Main Visual Aid	
OxyContin	11/19/2008	Call with FDA	Call to discuss the video titled, "Treating Chronic Pain" which appeared on a pregnancy blog and on Purdue's Partners Against Pain website.	PDD8013057484
OxyContin	11/25/2008	To FDA	<p>PPLP written response to the concerns expressed by DDMAC during the 11/19/08 phone call.</p> <ul style="list-style-type: none"> • Video was removed from the Partners Against Pain website about an hour after the end of the 11/19/08 call. PPLP temporarily shut down their non-branded websites while a comprehensive review of the non-branded materials was being performed. • "PPLP is developing a process for the efficient and comprehensive review of all non-branded material. These 	PURCHI-000835404

			<p>activities have been initiated and are expected to complete within a few weeks. Only after non-branded materials have been reviewed and found to be in compliance with the our discussion will the websites be re-activated.”</p> <ul style="list-style-type: none"> • “PPLP has begun discussions with outside firms to determine how we can monitor if our material has been placed on unauthorized websites.” • It appears the video link was copied from an authorized website and placed on the pregnancy blog without the knowledge or consent of PPLP. 	
OxyContin	12/3/2008	To FDA	<p>Submission of the following promotional items for review: Crime Stoppers Release – Spokane, WA Pharmacy Multi Robberies, Crime Stoppers Release – Kent, WA, Puget Sound, Crime Stoppers Release – Des Moines, WA – Puget Sound, Crime Stoppers Release – Everett, WA – Puget Sound, OxyContin \$60 Patient Savings Card Extension Flyer, \$60 Savings Card Pharmacist Instruction Info Sheet, Update Vermont Disclosure Forms – OxyContin, Drug Diversion in the Community Pharmacy – NCPA One – Time Presentation, Pharmacy Safety and Security Presentation, Brief Case History of the OxyContin Tablets, Revised \$60 Patient Savings Cards with New Expiration Date, Update Rx Products Section of Purdue Website, Crime Stoppers Release – Everett, WA Arrest, Price Increase Packages for Hospitals/Govt Hospitals, Price Increase Packages for Puerto Rico Chains, Price Increase Packages for Puerto Rico Wholesalers</p>	PURCHI-000835224
OxyContin	12/5/2008	From FDA	<p>Letter from the FDA with the minutes from the 11/19/08 phone call with PPLP to discuss a video titled “Treating Chronic Pain,” which appeared on a pregnancy wellness blog on Purdue’s Partners Against Pain website.</p> <p>Discussion Points</p> <ul style="list-style-type: none"> • “DDMAC stated that it considers the video a branded promotional piece because the video is clearly sponsored by Purdue and contains numerous efficacy claims about 	PURCHI-000835407

			<p>opioids, including oxycodone...”</p> <ul style="list-style-type: none"> • “DDMAC further stated that the video fails to communicate any risk information related to OxyContin, including the Boxed Warning. Additionally, the video broadens the indication for OxyContin by failing to disclose its full indication, including the limitations to the indication. DDMAC stress that this video is particularly concerning from a public health perspective because OxyContin has potential for abuse and has risks associated with its use that are serious and potentially fatal.” • “DDMAC also expressed concern about placing the video on a pregnancy blog webpage. OxyContin has teratogenic effects, and women who are, or are planning to become, pregnant should consult their physician before using this drug product...” • “...Purdue communicated that it did not intend the video to be a promotional piece for OxyContin, but instead a general discussion about opioid treatments. Additionally, Purdue stated that it was not responsible for placing the video on the pregnancy blog webpage, and it is impossible for Purdue to control the content on this blog.” • “...DDMAC reemphasized that the video was extremely problematic from a public health perspective and restated the same concerns as captured above. In addition, DDMAC expressed further concern that the video was able to be placed on a webpage that Purdue does not have control over.” <p>Action Items</p> <ul style="list-style-type: none"> • PPLP will contact FDA by 11/20/08 to confirm the video has been removed. • PPLP will review all materials in the public domain to ensure they do not have issues similar to those listed above 	
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			<ul style="list-style-type: none"> • PPLP will request comments from DDMAC on pieces/issues they have questions about • PPLP will look into ways to prevent their materials from being published on inappropriate sites • PPLP will submit a written response addressing these issues <p>Follow-up Items Purdue followed up with DDMAC on 11/20/08 and stated it has completed the following:</p> <ul style="list-style-type: none"> • Video was taken down from the Partners Against Pain website • PPLP has begun review of all its other pieces to make sure they don't contain any of the concerns expressed by DDMAC. • Purdue is seeing what technology can be used to prevent others from using their materials without permission • Purdue stated it would submit a written request within a week 	
OxyContin	12/12/2008	To FDA	Contents Not Reported	Bates Unavailable
Oxycontin	12/18/2008	From FDA	Contents Not Reported	Bates Unavailable
OxyContin	12/22/2008	To FDA	PPLP's letter regarding the investigations into the internet blog that contained the "Treating Chronic Pain" video discussed at the 11/19/2008 call.	PDD8013057495
OxyContin	1/7/2009	To FDA	Request for more information	PPLPC01600009932
OxyContin	1/8/2009	To FDA	<p>PPLP's submission with requests for comments. "In this material, there are mentions of opioid pain medicines, generic names of various opioids and brand names of various opioids. The reason for these mentions is to provide specific examples of the type of products under discussion in the context of:</p> <ul style="list-style-type: none"> • Discussing abuse and diversion, are these mentions allowable? • Providing state and federal guidance documents, is Purdue allowed to distribute these documents? • Discussing products that may address opioid adverse events, is it permissible to list products that may cause the adverse event? <p>PPLP submits for review the following items</p>	Bates Unavailable

			<p>for comment:</p> <ul style="list-style-type: none"> • <u>Lawful Prescribing and Prevention of Diversion</u> – “material created by PPLP dealing with abuse and diversion of opioids that is directed towards or distributed only to law enforcement audiences” (Attachment 1) • <u>Lawful Prescribing and Prevention of Diversion</u> – “material created by PPLP dealing with abuse and diversion of opioids that is directed towards or distributed to healthcare professionals...” (Attachment 2) • <u>Painfully Obvious</u> – “material created by PPLP dealing with abuse of drugs, including opioids, that is presented to consumers...” (Attachment 3) • <u>Prescription Drug Abuse Prevention Strategizer</u> - “material not created by PPLP dealing with abuse of drugs, including opioids, that is presented to consumers...” (Attachment 4) • <u>State and federal guidelines</u> – “material not produced by PPLP that is presented to healthcare professionals and may mention opioids in general...as a tool to promote appropriate and effective management of pain management.” (Attachment 5) • <u>Brochure on how to store medications</u> – “material not produced by PPLP, that is presented to healthcare professionals for distribution to their patients and may mention opioids in general...” (Attachment 6) • <u>Senokot drug listing</u> - “material posted on Purdue website or distributed by Purdue sales representatives that deals with over-the-counter medications” (Attachment 7) • <u>Press-Release on Survey of Pain in America</u> • (Attachment 8) 	
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OxyContin	1/16/2009	From FDA	Letter from the FDA with the revised minutes from the 11/19/08 phone call with PPLP to discuss a video titled "Treating Chronic Pain," which appeared on a pregnancy wellness blog on Purdue's Partners Against Pain website. Same as the previous minutes expect for the below addition: <ul style="list-style-type: none"> "DDMAC notes that according to Purdue's written response to DDMAC dated December 12, 2008, based upon its investigation, it appears that the link to the "Treating Chronic Pain" video was copied from an authorized website to http://pregnancywellnessblogspot.com without the knowledge or consent of Purdue Pharma L.P." 	PURCHI-000834901
OxyContin	1/19/2009	From FDA	Contents Not Report	Bates Unavailable
OxyContin	1/25/2009 or 1/26/2009	To FDA	Contents Not Report	Bates Unavailable
OxyContin	1/29/2009	To FDA	Contents Not Report	Bates Unavailable
OxyContin	2/3/2009	To FDA	Contents Not Report	Bates Unavailable
OxyContin	2/25/2009	To FDA	Contents Not Report	Bates Unavailable
OxyContin	4/13/2009	Call with FDA	Contents Not Report	Bates Unavailable
OxyContin	4/14/2009	To FDA	Contents Not Report	Bates Unavailable
OxyContin	4/16/2009	To FDA	Letter to the FDA advising that per their request, PPLP is withdrawing Appendix 8 of the 1/7/09 advisory submission	PURCHI-00835490
OxyContin	5/26/2009	To FDA	PPLP follow up to 2/25/2009 submission with a draft visual aid for review.	PPLPC001000069460
OxyContin	9/21/2009	To FDA	Submission of the following promotional items for review: Email message 9/24/09 FDA Advisory Committee Meeting, ASPMN Cyper Café Kiosk OxyContin Panel with Boxed Warning, Indications and Usage, Options Logo and Boxed Warning on Plasma Wall at National Conventions, American Academy of Physician Assistants (AAPA) Thank you Letter-Product Theater Attendees, Options Campaign Panels for National Conventions-Interior One Panel and Interior Two Panels, Update Vermont Pricing Disclosure Forms, New OxyContin Options 2-Page Journal Ad, Options Campaign Panels for National Conventions – Outside Column Panel and NACD Custom	PDD8013315785

			Panel	
OxyContin	12/24/2009	From FDA	<p>FDA's response to PPLP's 1/8/2009 request for comments on materials that PPLP distributes as part of its risk management efforts.</p> <p><i>Lawful Prescribing and Prevention of Diversion (Attachment 1)</i></p> <ul style="list-style-type: none"> “...you state that attachment 1 is directed towards or distributed only to law enforcement audiences. However, slide 6 of the attachment states that ‘The intent of this program is to educate healthcare professionals and law enforcement officials...’ <p><i>Lawful Prescribing and Prevention of Diversion (Attachment 2)</i></p> <ul style="list-style-type: none"> The boxed warning “omits risk information from the boxed warning” in the PI. “Specifically, the boxed warning from its PI includes the following information, ‘OxyContin Tablets are NOT intended for use as a prn analgesic...’ DDMAC recommends revising...to include this risk information” <p><i>Painfully Obvious (Attachment 3)</i></p> <p>Broadening of Indication</p> <ul style="list-style-type: none"> Claim: “Opioid analgesics are pain relief medications...They provide relief to people who are experiencing pain due to disease, injury or surgery....” FDA Response: “These claims are misleading because they suggest that OXYCONTIN is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence...DDMAC recommends revising these claims and presentations to be consistent with the PI.” <p>Minimization/Omission of Risk</p> <ul style="list-style-type: none"> Claim: “When opioids are used properly...they are usually effective at relieving pain. They may cause <u>side effects</u> such as drowsiness, nausea, vomiting, itching, headache, 	PPLPC001000052249

			<p>dry-mouth, sweating, and constipation. When opioids are <u>misused</u>, or abused, in addition to side effects, they can cause more serious problems such as extremely slow breathing and death.” FDA Response: “These claims are misleading because they omit serious and potentially fatal risks that are associated with opioids including OXYCONTIN, and they minimize the risks presented by implying that serious side effects can only occur if the drug is misused or abuse, when this is not the case.”</p> <p>Overstatement of Efficacy</p> <ul style="list-style-type: none"> Claim: “Prescription medications are invaluable for people with certain medical conditions and even saves lives.” FDA Response: “This claim...misleadingly overstates the efficacy of the products listed, including OXYCONTIN, by implying that OXYCONTIN has been shown to save lives, when this is not the case. DDMAC recommends eliminating such misleading claims.” <p><i>Attachments 4 through 7</i></p> <ul style="list-style-type: none"> DDMAC had no further comments 	
OxyContin	2/24/2010	To FDA	Contents Not Report	Bates Unavailable
OxyContin	3/19/2010	From FDA	<p>FDA’s response to PPLP’s submission from 2/14/2010.</p> <p>General Comments</p> <ul style="list-style-type: none"> The proposed field card is based on the draft product labeling. “We remind Purdue that the proposed field card and any other materials that include a representation about OxyContin should be revised to be consistent with the approved PI.” <p>Broadening of Indication</p> <ul style="list-style-type: none"> Claim: “OxyContin Tablets are indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended 	PDD8013314665

			<p>period of time.” FDA Response: “This presentation is misleading because it suggests that OxyContin is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence.”</p> <ul style="list-style-type: none"> DDMAC acknowledges that the full indication is presented at the bottom of page 2 but this doesn’t mitigate the misleading implication. <p>Minimization/Omission of Risk</p> <ul style="list-style-type: none"> “The proposed field card fails to include risk information in each specific part as necessary to qualify the safety and effectiveness claims of OxyContin. Risk information should appear in the same parts of the piece as the benefit information...” <p>Misleading Presentation</p> <ul style="list-style-type: none"> Claim: “While similar in appearance to the original formulation, the reformulated tablet: 1. Is slightly larger in size than the currently marketed tablets;...” FDA Response: Claim is “misleading because it implies that all of the reformulated tablets are larger in size than the corresponding original formulation.” 	
OxyContin	3/24/2010	To FDA	PPLP submits a draft sales field card [version 2] for review and comment	PPLPC016000015109
OxyContin	3/28/2010	To FDA	PPLP submits a revised draft sales field card after the FDA’s comments on 3/29/2010.	PDD8013315259
OxyContin	3/30/2010	From FDA	<p>FDA’s response to PPLP’s 2/24/2010 request for comments regarding the proposed launch materials for OxyContin.</p> <p>General</p> <ul style="list-style-type: none"> “DDMAC notes that the proposed statement and questions are based on draft product labeling (PI). We remind Purdue that the proposed statement and questions and any other materials that include a representation about OxyContin should be revised to be consistent with the approved PI.” “DDMAC reminds Purdue that if part of the intended audience for the 	PDD8013315267

			<p>proposed statement and questions is <i>consumers</i>, the proposed materials should also present the indication and important risk information in consumer-friendly language.”</p> <p>Broadening of Indication</p> <ul style="list-style-type: none"> • Claims: “OxyContin tablets are indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time” and “OxyContin is a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.” FDA Response: Claims are misleading “because they suggest that OxyContin is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence.” <p>Omission/Minimization of Risk</p> <ul style="list-style-type: none"> • “...we note that the proposed statement omits the contraindications, warnings and precautions, and the most frequently reported adverse reactions as presented in the PI and the proposed questions entirely omit important risk information. Additionally, we note that the proposed statement fails to present risk information (e.g., Boxed Warning) in conjunction with claims relating to the effectiveness of the drug.” <p>Misleading Presentation</p> <ul style="list-style-type: none"> • Claim: “While similar in appearance to the original formulation, the reformulated tablet is slightly larger in size and has a different marking (“OP”) than the currently marketed tablets (marking “OC”).” FDA Response: “The proposed claim is misleading because it implies that all of the reformulated 	
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			tablets are larger in size than the corresponding original formulation.”	
OxyContin	4/21/2010	From FDA	FDA’s response to PPLP’s 3/28/2010 submission. DDMAC had no further comments.	PDD8013315370
OxyContin	2/3/2011	To FDA	Submission of the following promotional items for review: Conversion/Titration guides, eDetail Printed Rep Invitation, eMail Survey Program, HCP Portal Printed Rep Invitation, IASP Product Theater Presentation, Tablet photos – PDR, RM Pilot Conversions Experience	PKY183134676
OxyContin	2/15/2011	To FDA	Submission of the following promotional items for review: Relationship Marketing eMail 4 (confidence) (5 variable subject lines), Relationship Marketing eMail 4 (delayed) (4 variable subject lines), Relationship Marketing eMail 5 (confidence) (2 variable subject lines), Relationship Marketing eMail 5 (delayed) (2 variable subject lines), Relationship Marketing eDetail 3, Relationship Marketing eDetail 3 Invitations (5 variable subject lines) Relationship Marketing eDetail Invite (5 variable subject lines), Video – Dr. Cole, Video – Dr. Gudin, HUD Fact Sheet, Relationship Marketing Conversions Invitation, Relationship Marketing Search Engine terms, Relationship Marketing eDetail Invite for Doctor Directory (3 variable subject lines), Relationship Marketing WebMD email, Relationship Marketing eDetail 6 (confidence), Relationship Marketing eDetail 6 (delayed) (2 variable subject lines)	PKY183135295
OxyContin	6/30/2011	To FDA	Submission of the following promotional items for review: ORF Patient Letter/Med Guide/FPI for GPOs and MCO Mail Order, RM eDetail #2 Invitations, Reformulation Medication Guide – Spanish, VT Pricing Forms, Confident Treater Segmentation Flashcard, Delaying Treater Segmentation Flashcard, ASPMN – Thank You Letter + FPI OxyContin Product Theater, 2011 OxyContin Patient Savings Cards, PG Dinner Invites_PractApps, PG Webconference Confirms and Thank You, Journal Ad, Patient Savings Card, Main Vis Aid Interactive Media Horizontal, ORF REMS Website, Price Documents – March 2 – Various Rx, PG-OC_PractApps_20 –	PKY183135481

			Recruitment script, PG-OC_PractApps_Dinner_Confirm-Thanks_6-8, PG-OC_PractApps_Webconf_Confirm-Thanks_16-18, \$70 Savings Card Instruction Sheet, RM Pilot Detail #2, PG-OC_PractApps_Webconf_Invites_11-15, RM Pilot Conversions Experience	
OxyContin	10/17/2011	To FDA	Submission of the following promotional items for review: Product Theater Slide Deck – Kate – Low Back Pain, Fact Sheet Version 2011, OTR3001 Dear Colleague Letter, OTR 3001 Cocoon Study Press Release, PainWeek Data Standby Statement, AAFP OxyContin Product Theater Electronic Poster, AAFP OxyContin Product Theater Printed Poster, AAFP OxyContin Product Theater Room Drop/Invitation, OxyContin Local Exhibit Graphic Panel, IVR Flow Sheet and Triple I Customer Service Reference/FAQ Script for Call, Slim Jim, Confident Treater Segmentation Flashcard, Delaying Treater Segmentation Flashcard, VT Pricing Forms	PKY183136309
OxyContin	12/16/2011	To FDA	Submission of the following promotional items for review: Revised OxyContin Fingertip Formulary Templates, ACNP OxyContin Product Theater Thank You Letter, ACNP OxyContin Welcome Letter Packet, ACNP OxyContin Product Theater Room Drop Invitation, ACNP OxyContin Product Theater Printed Poster, ACNP OxyContin Product Theater Electronic Poster, AAFP OxyContin Product Theater Thank You Letter, AAFP OxyContin Product Theater Welcome Letter & Packet, AAPM&R OxyContin Product Theater Invitation/Room Drop, AAPM&R OxyContin Product Theater Electronic Poster, AAPM&R OxyContin Product Theater Welcome Letter & Packet, AOA OxyContin Product Theater Room Drop Invitation, AOA OxyContin Product Theater Printed Poster, OxyContin Main Visual Aid, OxyContin RM Pilot Conversions Laptop, OxyContin RM Pilot Conversions Experience, VT Pricing Forms, Core Visual Aid – People, Slim Jim – People, Member Health Formulary Announcement Program	PKY183136487
OxyContin	3/23/2012	To FDA	Submission of the following promotional items for review: Savings Card Program, Pharmacy Benefit Manager, AAPM&R	PKY183136836

			Product Theater Printed Poster, RM Pilot eDetail #1, RM Pilot eDetail #2, RM Pilot eDetail #3, AAPM&R Product Theater Thank You Letter, eDetail HCP eMail Invitation, RM Conversions eMail Invitation, Conversion and Titration Guide, Information Sheet: Second Printing of 2011 OxyContin Savings Card Program, IVR Flow Sheet and Triple I Customer Service Reference/FAQ Script for Calls, Convention Panel A, B, C, D, E, F, G, H, and I, PurdueHCPOxyContin pages, Journal Ad, A Journal Ad, King size Journal Ad	
OxyContin	4/5/2012	To FDA	Submission of the following promotional items for review: Real Talk email and Survey #6, Managed Care Coverage Direct Mail Campaign, Managed Care Formulary Coverage Email Campaign, Real Talk email and Survey #5, Email Trigger Letters, Target email #2, Target email, Representative Trigger Letters, Real Talk email and Survey #4, VT Pricing Forms, Real Talk email #2 and Survey, Real Talk email #3 and Survey, Updated Fingertip Formulary Templates, Digital Savings Card Recruit Emails, Portal Recruit Email, Real Talk Email #1 and Survey, Convention Panel I, RM eDetail #2 Invitations, Keywords and ads	PKY183137274
OxyContin	4/20/2012	To FDA	Submission of the following promotional items for review: Spanish IVR and FAQ Savings Card Program, Spanish Savings Card Instruction Sheet, Updated OxyContin Single Channel Fingertip Grid, Updated Fingertip Formulary Templates, OTR3001 Dear Colleague Letter, Target email 3, Target email 4, Conversion Direct Mail Waves 2 and 3, Conversion Direct Mail Wave 1, VT Pricing Forms, Wave 1: Confident and Delaying Treater Segmentation Mailers, Segmentation Mailers Wave 2 and 3 Direct Mail Campaign, Real Talk email and survey #6, Demystifying Opioid Conversion Calculations FMRI Disclaimer Sticker, Demystifying Opioid Conversion Calculations Front of Book/Back of Book	PKY183137405
OxyContin	6/4/2012	To FDA	Submission of the following promotional items for review: Conversion and Titration Guide, Core Message Leave Behind, A-size Journal Ad, Nominated Speaker Letter, Group DCA invites to eDetail #2, Group	PKY183137568

			DCA invites to eDetail #1, ORF tamper simulation video, ORF Epi Studies Press Release – American Pain Society	
OxyContin	6/21/2012	To FDA	Submission of the following promotional items for review: Banner Ads	PKY183137670
OxyContin	7/03/2012	To FDA	Submission of the following promotional items for review: A Size Journal Ad, Vermont Pricing	PKY183137722
OxyContin	8/23/2012	To FDA	Submission of the following promotional items for review: VT Pricing Forms, CVS/Caremark/Silverscript Part D Formulary Win Announcement email, Doctor Directory OxyContin Vendor emails, Quantia Conversions, Quantia Conversions Part 1 Mobile Optimization, Trigger Invitations, Common Errors Document, REMS Statement_070912, REMS Statement_070912 Internet, Epocrates Formulary Flash, Quantia Conversions versions 2-4	PKY183137729
OxyContin	10/11/2012	To FDA	Submission of the following promotional items for review: Fingertip Formulary Template, Savings Program Detail Sheet, AOA Product Theater Invitation/Room Drop, IVR Flow Sheet and Triple I Customer Service Reference/FAQ Script for Calls, Field Card, AAFP Product Theater Invitation/Room Drop, Appropriate Patient Care Vignettes, ORF Epi Studies IASP Press Release, Single Channel Fingertip Formulary Grid T3 2012, Fall 2012 Journal Ad – A size, REMS Website, VT Pricing Forms	PKY183138686
OxyContin	12/20/2012	To FDA	Submission of the following promotional items for review: ORF Tamper Simulation Video, AOA Product Theater ePoster, AOA Product Theater Printed Poster, Local Exhibit Display Panel, Convention Panel G, AOA Product Theater Welcome Letter, Practical Pain Management Vendor Version of Savings Card Email, Medscape OxyContin Savings Card email, Field Card, AOA Product Theater Thank You Letter, AAFP Product Theater ePoster, Medicare Part D Formulary Coverage email campaign, AAFP Product Theater Welcome Letter, AAFP Product Theater Printed Poster, Reformulation Information for Federal/State Govt, Slide Deck (Barbara), Convention Panel H 2012 Fall Update, eDetail eMail Invitations, 2012 Mid-Year OxyContin Sales Aid, King Size Journal Ad – 2 pg brief,	PKY183138789

			AAFP Product Theater Thank You Letter, Panel at Natl Conv 54x46, Common Errors Document, No See HCP Savings Card Letter, Updated PI for ePocrates Formulary Flash, Journal of Pain ORF Study November 2012, Journal of Pain Pitch Email and Script	
OxyContin	1/28/2013	To FDA	Submission of the following promotional items for review: Target email 4, Target email, Savings Program Detail Sheet, Portal Recruit Email, VT Pricing Forms, F8287-FT 12/12 Announcement Card Template, PTN Video Script – Fall 2012, Patient Essentials Information Pack – Individual Kit Packaging, Patient Essentials Information Pack – Housing, PTN Video – Dec 2012, Wholesaler Fact Sheet, PTN Program Invitation 2012, Savings Card Program, Savings Card Program HCP Information Sheet, 2012 Trigger Mail Program, Core Visual Aid – Spring 2013, Patient Essentials Information Pack – Pain Tracker, Patient Essentials Information Pack – Welcome Brochure, 2013 Savings Card Brochure, Conversion and Titration Guide – Spring 2013	PKY183139077
OxyContin	3/07/2013	To FDA	Submission of the following promotional items for review: VT Short Form Templated Letter to ASF Representatives Covering VT HCPs, Seasonal eMail 1: New Year/Savings, Spanish IVR and FAQ for Savings Card Program, Target Email 3, Target Email 2, IVR Flow Sheet and Triple I Customer Service Reference/ FAQ Script for Calls, Statement on FDA Guidance for Developing Abuse Deterrent Opioid Formulation, Statement on FDA Response to Cit Petition FDA-2012-P-0929 1 29 13, 2013 Trigger Email Campaign, Fall 2012 Slim Jim, Savings Card Recruitment eMail, VT Pricing Forms, Journal Ad – Digest, A Size Journal Ad – 2 page creative 2 page BS, No See HCP Savings Card Letter	PKY183139295
OxyContin	3/27/2013	To FDA	Submission of the following promotional items for review: Real Talk eMail Series and Surveys – Savings Program Updates, QuantiaMD Savings Program, Animated Banner Ads-7/12 Label Updates, PurdueHCP.com OxyContin: S.T.A.R.T. Principles, King Size Journal Ad – 2 pg brief, Target email 1	PURCHI-000531139
OxyContin	4/10/2013	To FDA	Submission of the following promotional	PKY183128472

Butrans			items for review: Genuine Product Identification Guide, PurdueHCP.com home page redesign, OxyContin, Butrans, and Intermezzo, Butrans/OxyContin Virginal Mason 'No See' Email Letter	
OxyContin	4/11/2013	To FDA	Submission of the following promotional items for review: Tablets Packaging Change Visual Aid, Formulary Grid, Savings Card Expiration, Formulary Grid Medicare	PKY183139458
OxyContin	4/25/2013	To FDA	Submission of the following promotional items for review: Label Change Press Release	PKY183141204
OxyContin Butrans	5/24/2013	To FDA	Submission of the following promotional items for review: P-Kinect Interactive Media – Butrans, OxyContin, OTC, Genuine Product Identification Guide – CBP version	PKY183129029
OxyContin	6/3/2013	To FDA	Submission of the following promotional items for review: Patient Case Vignettes for iPad, Pharmacy Benefit Manager Piece, Relationship Marketing Program Invitations, Pharmacist Guide, VT Pricing Forms, Actavis Announcement	PKY183139559
OxyContin	6/14/2013	To FDA	Submission of the following promotional items for review: Spanish IVR and FAQ for Savings Card Program	PKY183139794
OxyContin	6/19/2013	To FDA	Submission of the following promotional items for review: King Size Journal Ad Spring 2013, Medicare Part D Ad with Brief Summary of Prescribing Information, A-size Journal Ad Spring 2013, Labeling Update: Purdue Press Release Email, Managed Care Reminder eMails: Commercial and Medicare Part D, Savings Program Reminder Email: Eligible Patients in Massachusetts	PKY183139833
OxyContin	7/11/2013	To FDA	Submission of the following promotional items for review: Label Change Sales Aid, Seasonal: eMail 2, Paid Search Campaign: Keywords and Ad Copy, Journal Ad – Digest, Custom Formulary Grid – Commercial	PKY183139881
OxyContin	7/25/2013	To FDA	Submission of the following promotional items for review: Labeling Updates: 3 eMails, Account Executive Slide Deck, CPDD 2013 KY Poster Pitch Materials	PKY183139943
OxyContin	8/13/2013	To FDA	Submission of the following promotional items for review: PurdueHCP.com: OxyContin Labeling Update, Formulary, and Savings Card Pages, Banner Ads re: Updated Labeling, Electronic Leave Behind-Use for Approved Labeling Update eMails, 10' Hanging Sign Exhibit Booth, Convention	PKY183140033

			Panel	
OxyContin	9/13/2013	To FDA	Submission of the following promotional items for review: PurdueHCP.com: OxyContin ISI page, PDR Brief: Electronic Medical Record Display, Custom Formulary Grid Med-D, Additional Patient Case Vignettes, Reformulation Information for Federal and State Govt, VT Pricing Forms, Core Visual Aid – Spring 2013, Conventional eMail Template	PKY183140131
OxyContin Butrans	9/27/2013	To FDA	Submission of the following promotional items for review: 15 mcg/hour Convention Panel, 15 mcg/hour Decision Tree, 15 mcg/hour Patient Profile – Kathy, 15 mcg/hour Flashcard, 15 mcg/hour Initiation & Titration Guide, Focused Issue Brochure: Patient Access, Journal Ad: King Size, 15 mcg/hour Patient Brochure, Patient (Information Guide) Brochure for Website Use, Nominated Speaker Letter, Journal Ad: Digest, Conversion Tool on Butrans.com, 15 mcg/hour Announcement eMail, OxyContin & Butrans Nominated Speaker Letter	PURCHI-003256695
OxyContin	10/24/2013	To FDA	Submission of the following promotional items for review: Labeling Update eMail: PTJournal Vendor Version, Labeling Update ASF Representative Trigger Letters	PKY183140349
OxyContin	11/11/2013	To FDA	Submission of the following promotional items for review: Patient Essentials Pack eMail, Trigger Emails	PKY183140405
OxyContin	11/26/2013	To FDA	Submission of the following promotional items for review: 2013 Generic Contingency Savings Card Brochure (stand-alone)	PKY183140450

Promotional Material Review & DDMAC Discussions

PURDUE				
Product	Date	To/From FDA	Contents	BATES
Butrans	12/17/2009	To FDA	Submission of APS Press Release – Purdue Pharma LP Presents Phase 3 Study of Transdermal Delivery of Buprenorphine in Moderate to Severe Pain	PPLP004167649
Butrans	6/24/2010	To FDA	Contents Not Report	Bates Unavailable
Butrans	6/29/2010	From FDA	<p>FDA’s response to PPLP’s 6/24/2010 submission requesting advisory comments on a proposed press release for Butrans.</p> <p>General Comments</p> <ul style="list-style-type: none"> • “We remind Purdue that the proposed press release and any other promotional materials that include a representation about Butrans should be updated to accurately reflect the final approved PI.” • “DDMAC notes that the proposed press release makes reference to other formulations, and indications for buprenorphine...DDMAC reminds you that misbranding another company’s product will misbrand Butrans and recommends eliminating the claims.” <p>Omission of Material Fact</p> <ul style="list-style-type: none"> • “The proposed press release fails to reveal any of the serious risks presented in the WARNINGS AND PRECAUTIONS section of the full PI...DDMAC recommends revising these claims to include this important material information in direct conjunction with these claims.” <p>Minimization of Risk</p> <ul style="list-style-type: none"> • “The sequence of risk information presented in the proposed press release misleadingly minimizes the risks associated with Butrans...We recommend revising the sequence of this presentation to disclose the most serious risks first.” • “Furthermore, the relegation of risk information to the end of the proposed press release misleadingly minimizes the risks associated with Butrans. DDMAC recommends revising the proposed press 	PPLP004167831

			<p>release in a manner that presents important risk information with comparable prominence to efficacy claims taking into account all techniques apt to achieve emphasis.”</p> <ul style="list-style-type: none"> • “The presentation of the risk information within the proposed press release minimizes risks associated with Butrans.” <p>Lack of Contextual Information</p> <ul style="list-style-type: none"> • “We note that the section of the proposed press released titled, ‘Clinical Trial Experience’ omits important contextual information relating to clinical trials...These claims misleadingly omit important contextual information regarding the clinical studies submitted to FDA...we recommend revising these claims in a manner consistent with the PI, including all important contextual information.” <p>Misleading Claims</p> <ul style="list-style-type: none"> • Claim: “Healthcare professionals now have an important option for adult patients suffering from moderate to severe chronic pain for whom NSAIDs or acetaminophen are no longer options and an opioid may be needed to manage their pain.” FDA Response: “This claim is misleading because it implies Butrans is an appropriate option for use in all instances or adult patients with moderate to severe chronic pain for whom NSAIDs or acetaminophen are no longer options, and many need an opioid for pain management, when this is not the case. Specifically, Butrans is not interchangeable with NSAIDs, acetaminophen or other opioids since there are differences in the drugs’ indications, dosing, safety, and efficacy.” • “...DDMAC notes that the claim misleadingly implies that treatment with Butrans eliminates the need for NSAIDs, acetaminophen, and other opioids, when this is not the case.” • Claim: “Butrans Transdermal System has been used clinically outside the United States since 2004, and it is 	
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currently marketed...in 16 countries....”
FDA Response: “This claim and similar claims are misleading because they suggest that Butrans has a history (i.e. ‘6 years’) of proven efficacy and safety, when this not necessarily the case. The standards under which a drug is approved differ among regulatory bodies in different countries. Thus, to make a claim suggesting that a drug has been proven safe and effective under standards that may differ from those used in the U.S. by FDA standards misleadingly suggests that Butrans’ safety and efficacy profile has been known for over 6 years, when his is not necessarily the case.”

Unsubstantiated Superiority Claim

- **Claim:** “First and Only Opioid Analgesic Product that Delivers Continuous Release of Medication Over Seven Days.” **FDA Response:** “This claim, although accurate, in the context of the proposed press release is misleading because it implies that Butrans provides superior analgesia to other opioid analgesic products, when such has not been demonstrated by substantial evidence.”

Broadening of Indication

- **Claim:** “PURDUE PHARMA L.P. RECEIVES FDA APPROVAL FOR BUTRANS (buprenorphine) TRANSDERMAL SYSTEM CIII FOR PAIN MANAGEMENT” and “First and Only Opioid Analgesic Product that Delivers Continuous Release of Medication over Seven Days.” **FDA Release:** “The totality of these claims in the context of the proposed press release misleadingly suggests that Butrans is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence...DDMAC recommends revising these claims to present the full indication in conjunction with and with comparable prominence to initial claims of efficacy and whenever the indication for Butrans is presented.”

Butrans	7/20/2010	To FDA	PPLP provides introductory promotional materials for Butrans consisting of a journal ad and sales ad.	PPLP004167948
Butrans	8/20/2010	From FDA	<p>FDA's response to PPLP's 7/20/2010 submission requesting comments.</p> <p>General Comments</p> <ul style="list-style-type: none"> “Butrans is the first and only prescription opioid analgesic drug that provides systemic delivery of buprenorphine continuously for 7 days. When another opioid analgesic drug with the above characteristics and indication is approved, derivative claims promoting market exclusivity, would be misleading.” <p>Omission of Material Fact</p> <ul style="list-style-type: none"> “Although the proposed journal ad presents some of the warnings and precautions from the highlights section of the approved product labeling (PI), it fails to reveal other serious risks and material information associated with the use of Butrans.” <p>Unsubstantiated Superiority Claims</p> <ul style="list-style-type: none"> Claim: “Butrans is doses less frequently than immediate- or extended-release opioids.” FDA Response: “Within the context of the branded journal ad, this claim and similar comparative claims are misleading because they imply that because the formulation allows for less frequent dosing, Butrans is superior to other opioid analgesic products, in the absence of substantial evidence or substantial clinical experience.” <p>Lack of Contextual Information</p> <ul style="list-style-type: none"> Claim: “The Butrans Transdermal System-the first and only 7-day analgesic delivered in <u>one application</u>,” and “<u>One Butrans, Once Weekly</u>” FDA Response: “These claims and similar claims and presentations misleadingly omit important contextual information regarding the dosing and administration of Butrans.” Claim: “<u>Evaluated</u> safety and <u>efficacy</u>. Dosed every 7 days, Butrans has been 	PPLP004168046

			<p>evaluated for safety and efficacy in both <u>opioid-naïve and opioid-experienced patients.</u> FDA Response: “This and similar claims are misleading because they omit important contextual information regarding the efficacy results, the patient population, and the clinical studies used to support the approval of Butrans.” Such claims are “misleading because they omit important contextual information regarding the dosing of Butrans in these patients.”</p> <p>Communication</p> <ul style="list-style-type: none"> • Statement: “Please read Brief Summary of Full Prescribing Information on the following pages and Contraindications on adjacent page.” FDA Response: “DDMAC recommends revising the statement to adequately signal the reader of the additional important risk information included in the adjacent page.” • Statement: “One Butrans – 7 days of analgesic delivery” FDA Response: “We recommend revising this presentation to present the full indication with comparable prominence to the efficacy claim, and whenever the indication for Butrans is prescribed.” 	
Butrans	9/23/2010	To FDA	Submission of the following promotional items for review: Butrans (buprenorphine) Transdermal System CIII 5, 10, and 20 mcg/hour pouch, ASP Product Theater Invitation – Room Drop, Press Release – Butrans FDA Approval, Branded FPI, Header at National Convention, E-Mail Management Web Content, Retail Sell Sheet, Information on website, IASP Product Theater Welcom Letter and FPI, IASP Product Theater Electronic Poster, IASP Product Theater Printed Poster, National Convention Panels, National/Int’l Convention Panel	PPLPC021000326470
Butrans	10/8/2010	To FDA	Submission of the following promotional items for review: 19” Monitor Screen Saver, 40” Monitor Screen Saver, Plasma wall panels, Product Theater Presentation – Dr. Hale, PAINWeek Product Theater Poster, PAINWeek Invitation/Room Drop, National Conventions Scrim	PPLPC002000083916
Butrans	10/28/2010	To FDA	Submission of IASP Convention Panel and	PURCHI-003238118

			National Convention Panel for review	
Butrans	11/4/2010	To FDA	Submission of Butrans Product Theater – Dr. Hale Presentation for review	PURCHI-003238168
Butrans	11/12/2010	To FDA	Submission of Managed Care Sell Sheet, Group Purchasing Sell Sheet, Health Alliance Email Press Release, and Medical Liaison Email Press Release for review	PURCHI-003238294
Butrans	12/2/2010	To FDA	Submission of the following promotional items for review: PDR Product Images, Room Drop Invitation 11/5/10, Room Drop Invitation 11/11/10, AOA Electronic Poster, ASCP Product Theater Slide Presentation, AAPM&R Product Theater Slide Presentation, Rebate Fact Sheet	PURCHI-003238500
Butrans	12/14/2010	To FDA	Submission of the following promotional items for review: www.butransrems.com website, HCP REMS Letter, HCP Training Guide, HCP Training Confirmation Form, REMS Folder, REMS Mailing Envelope	PURCHI-003238958
Butrans	12/23/2010	From FDA	<p>Response to PPLP's 7/20/2010 submission.</p> <p>Omission of Risk Information</p> <ul style="list-style-type: none"> “The proposed sales aid is misleading because it omits important risks associated with the use of Butrans.” DDMAC recommends revising the sales aid to include the important risk information on Butrans not being recommended for use in patients who have received MAO inhibitors within 14 days.” <p>Omission of Material Fact</p> <ul style="list-style-type: none"> The sales aid omits important risk information on the following: interactions with alcohol, CNS depressants, and illicit drugs, head injuries, hypotensive effects, application site skin reactions, use in pancreatic/biliary tract disease and other GI conditions, pediatric use <p>Minimization of Risk Information</p> <ul style="list-style-type: none"> Claim: “Adverse reactions reported in clinical trials were those <u>typically associated</u> with opioid therapy and transdermal formulations.” FDA Response: “This statement misleadingly minimizes the risks associated with Butrans...DDMAC recommends deleting this claim.” 	PPLP004168092

			<ul style="list-style-type: none"> • “The tab labeled ‘Safety’ misleadingly minimizes the risks associated with Butrans because it implies that this section of the sales aid contains a comprehensive list of the drug’s risk information. However, only some of the risks and common adverse reactions associated with Butrans are presented. We recommend revising this presentation to avoid this misleading implication and to be consistent with the full PI.” • “The proposed sales aid presents various efficacy claims for Butrans under bolded, colorful headers. In contrast, risk information is presented throughout the piece without a prominent call out to alert the reader of the risk information...DDMAC recommends that you revise the proposed sales aid to present risk information with a prominence and readability reasonably comparable to the efficacy claims, e.g. presenting a prominent call out to risk information.” <p>Unsubstantiated Superiority Claims/Overstatement of Efficacy</p> <ul style="list-style-type: none"> • Claims: “Butrans <u>is dosed less frequently than immediate- or extended-release opioids.</u>” “Butrans is unaffected by variables associated with <u>daily oral medications.</u> With Butrans, there is <u>no first-pass metabolism</u> and a patient may experience <u>few fluctuations</u> in plasma buprenorphine levels” and “Butrans is <u>dosed less frequently than immediate- or extended release opioids,</u> which may require repeat daily dosing for around-the-clock therapy.” FDA Response: “...these claims and similar comparative claims are misleading because they imply that because of its route of administration, pharmacokinetics, and dosing frequency, Butrans is superior to other opioid analgesic products or therapies, in the absence of substantial evidence or substantial clinical experience.” <p>Misleading Claims and Presentations</p>	
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- **Claim:** Aid includes “graphic representation of opioid receptor activity with buprenorphine shown as the partial agonist, and the Kappa antagonist, within the tab ‘MOA/Delivery System’...The analgesic activity of buprenorphine results primarily from binding to the mu opioid receptor.” **FDA Response:** “The totality of this claim and presentation is misleading because it suggests that Butran’s activity as a kappa antagonist has been prove to contribute to Butran’s analgesic effect, when such has not been demonstrated by substantial evidence.”
- **Claim:** “Only Butrans maintains a continuous 7-day delivery of analgesic medication.” **FDA Response:** “The claim and presentation are misleading because the graph depicts drug plasma concentration, not drug delivery.”
- **Claim:** “43 (4%) of 1,024 patients in the study population were 75 years of age or older” and “53 (5%) of 1,160 patients in the study population were 75 years of age or older.” **FDA Response:** “These claims misleadingly imply that 4% and 5% of the patients aged 75 years of age and older completed the open-label and double-blind periods of the clinical studies for Butrans when this is not the case.”
- **Claim:** “...sales aid prominently presents claims, graphs and efficacy data on the clinical studies for Butrans with bolded headers such as, ‘7-day Butrans delivers efficacy in opioid-naïve patients’ and ‘7-day Butrans delivers efficacy in opioid-experienced patients’ **FDA Response:** “In contrast, information about the clinical study in low back pain which failed to show efficacy is presented under the adverse reaction sections. DDMAC recommends revising this misleading presentation.”
- **Claim:** “...proposed sales aid presents efficacy results for Butrans in opioid-experienced patients and contains p-values, a bar graph of titled, ‘Patients reporting at least a 30% improvement in pain scores’ with a truncated y-axis, and the claim, ‘a 12-week multicenter,

randomized, double-blind, active comparator study to determine the efficacy, tolerability, and safety of Butrans 20 mcg/hour or active control vs. Butrans 5 mcg/hour in patients with moderate to severe chronic low back pain.” **FDA Response:** “These claims and presentations are misleading and inconsistent with the full PI for Butrans.”

Lack of Contextual Information

- **Claim:** “...the proposed sales aid presents a graphic of a shoulder and an arm with each of the seven days of the week printed in the area equivalent to where Butrans might be expected to be applied.” **FDA Response:** “These and similar claims and presentations misleadingly omit important contextual information regarding the dosing and administration of Butrans.”
- **Claim:** “....the proposed sales aid presents a bar graph depicting total buprenorphine exposures (AUC) following 7-day applications of Butrans 5 mcg/hour...” **FDA Response:** “This presentation is misleading because it omits contextual information from the PI regarding the study population.”
- **Claim:** “Start patients with mild to moderate hepatic impairment with the Butrans 5 mcg/hour dose. Butrans has not been evaluated in patients with severe hepatic impairment.” **FDA Response:** “This is misleading because it omits the following contextual information, ‘As Butrans is only intended for 7-day application, consider use of an alternate analgesic that may permit more flexibility with the dosing in patients with severe hepatic impairment...’”
- **Claim:** “...Thereafter and under supervision of the prescriber, the dose may be titrated to a level that provides adequate analgesia.” **FDA Response:** “This is misleading because it omits the following contextual information... ‘Thereafter, individually titrate the dose...to a level that provides adequate analgesia and minimizes side effects.’”

			<ul style="list-style-type: none"> • Claim: “For conversion from other opioids to Butrans, taper the patient’s around-the-clock opioids for up to 7 days to no more than 30 mg of morphine or equivalent per day before beginning treatment with Butrans...” FDA Response: “This claim and presentation misleadingly omits the following contextual information... ‘There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids.’” • Claim: “Patients initiated on Butrans 10 mcg/hour were tapered from their current opioid (30-to-80-mg morphine equivalent) during the phase 3 clinical trial...” FDA Response: “This claim is misleading because it omits important contextual information from the CLINICAL STUDIES section of the PI.” <p>Broadening of Indication</p> <ul style="list-style-type: none"> • Claim: “Once-weekly Butrans provides continuous delivery of buprenorphine and may be an alternative to other therapies” under the header, “Only Butrans maintains a continuous 7-day delivery of analgesic medication.” FDA Response: “The totality of this claim and presentation misleadingly implies that Butrans is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.” 	
Butrans	1/19/2011	To FDA	Submission of the following for review: FPI PDA Download, AOA Printed Poster, AOA Thank You Letter, ASCP Plasma Wall, ASCP Printed Poster, ASCP Thank you Letter, Govt Pricing Amendment, PAINWekk Poster	PPLP004171155
Butrans	1/28/2011	To FDA	Submission of Now Available Press Release, Fact Sheet, and Video News Release (Dr. Pergolizzi video/John Stewart video/manufacturing video) for review	PURCHI-003239506
Butrans	2/3/2011	To FDA	Submission of www.purduepharma.com for review	PKY183126707
Butrans	2/11/2011	To FDA	<p>PPLP’s request for clarification on comments made in the 12/23/2010 FDA response letter.</p> <p>Issue #1 – “One Butrans – 7 days of analgesic delivery”</p> <ul style="list-style-type: none"> • “We feel it is important to inform 	PPLPC001000079535

			<p>prescribers of the appropriate use of Butrans as an analgesic and that it is not for all approved indications of buprenorphine.”</p> <p>Issue #2 – “Butrans does not contain APAP, and NSAID, or a COX-II inhibitor”</p> <ul style="list-style-type: none"> “Especially given the recent action by FDA regarding restricting APAP doses in these agents, we feel that this is important safety information for prescribers. We did not mean to imply that these analgesic agents could not be used as supplemental analgesia to Butrans, nor that they have the same indication, and plan to add statements to that effect in association with this claim.” <p>Issue #3 – “For patients requiring around-the-clock therapy for an extended period of time, Butrans is dosed less frequently than immediate-or-extended release opioids.”</p> <ul style="list-style-type: none"> “...based on DDMAC’s belief that these are superiority claims, we feel that the first statement as listed in bold at the beginning of this paragraph, is a fixed feature of Butrans, and a factual statement that could remain. We believe that this statement lists how the drug is administered without claiming superiority or efficacy.” <p>Issue #4 – Deletion of p-values</p> <ul style="list-style-type: none"> “We would like to understand DDMAC’s position and reason for removing these p-values. Healthcare professional often ask questions regarding statistical significance of the data to ensure credibility of what is being presented” 	
Butrans	3/8/2011	To FDA	<p>Submission of the following promotional items for review: Patient Savings Program Activation Sticker, Patient Savings Program Brochure Holder, Patient Savings Program Brochure, Patient Savings Program Savings Card, Patient Savings Program Savings Card Brief Sheet, Journal Ad, Journal Ad – Digest, Journal Ad – Teaser page added, Journal Ad – King Size, Health Alliance REMS announcement eMail, Medial Liaison REMS announcement eMail,</p>	PURCHI-003241619

			Hospital/Govt Price Sheet, Puerto Rico Chain/Wholesaler Price Sheet, Wholesaler/Chain Price Sheet, APHA Banner Ad, Commercial Product Overview, MD Alert Letter, Pain week Press Release, Patient Brochure, Pharmacy Letter, Prescriber Fact Sheet, Rebate Fact Sheet, Retail Fact Sheet, Retain Visual Aid, Wholesaler Fact Sheet	
Butrans	3/21/2011	Call with FDA	<p>Meeting between Purdue and DDMAC to discuss comments from the 12/23/2010 advisory comments.</p> <p>During a 1/31/2011 phone call, Purdue asked for clarification on DDMAC's comments certain claims.</p> <p>Issue #1: "One Butrans – 7 days of analgesic delivery"</p> <ul style="list-style-type: none"> • PPLP Position: "intention...was not to imply efficacy, but to identify the drug class of Butrans as an analgesic, and to distinguish the product from other buprenorphine products approved for use in the maintenance treatment of opioid dependence." • FDA Response: "DDMAC noted that the claim itself links the pharmacokinetic element of the drug with the efficacy, and thus may misleadingly imply that adequate therapeutic effects are guaranteed to last for 7 days...Therefore, DDMAC maintains its position that the claim be revised to be consistent with the Pharmacokinetics section of the PI, i.e., replacing the word 'analgesic' with 'buprenorphine.'" • Resolution: - "Purdue will replace the term, 'analgesic' with buprenorphine' in the claim, 'One Butrans – 7 days of analgesic delivery.'" <p>Issue #2 – "Butrans does not contain APAP, and NSAID, or a COX-II inhibitor"</p> <ul style="list-style-type: none"> • Purdue's Position: "The purpose of including these ingredients...was to point out that Butrans is a single entity product which lacks any of these other analgesic agents that are included in other opioid formulation...The claim was not intended to imply that these analgesic agents could not be used as 	PPLP004168120

			<p>supplemental analgesia with Butrans, or that they have the same indication as Butrans.”</p> <ul style="list-style-type: none"> • FDA Response: “DDMAC maintains the position that this and similar claims misleadingly imply that Butrans is appropriate for use in all instances for which...APAP...NSAIDs, or...COX-II Inhibitors...are indicated, or that treatment with Butrans eliminates the need for NSAIDs, APAP, and COX-II inhibitors.” • Resolution: Claim was removed from all current promotional materials and references will not be made in future materials <p>Issue #3 – Inclusion of p-values</p> <ul style="list-style-type: none"> • Purdue’s Position: “Purdue pointed out that healthcare professionals often ask questions regarding statistical significance of the data to ensure credibility of claims and presentations.” • FDA Response: “...it is the Division of Anesthesia and Analgesia Products’ (DAAP) position that p-values be excluded from this promotional labeling.” • Resolution: “Purdue will eliminate the p-values from promotional materials in use...” <p>Issue #4 – “For patients requiring around-the-clock therapy for an extended period of time, Butrans is dosed less frequently than immediate-or-extended release opioids.”</p> <ul style="list-style-type: none"> • Purdue’s Position: “...the intention is to communicate that Butrans is dosed once a week, i.e., less frequently than other products such as immediate release opioids.” • FDA Response: “...this and similar comparative claims misleadingly imply that because of its dosing frequency, Butrans is superior to other opioid analgesic products or therapies... which are dosed more frequently. DDMAC considers it inappropriate to compare, and subsequently suggest superiority over products that have different indications or intended use.” 	
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			<ul style="list-style-type: none"> Resolution: Purdue will change their promotional materials 	
Butrans	5/20/2011	To FDA	Purdue requests two changes to the meeting minutes from 3/31/2011.	PPLP004168136
Butrans	5/25/2011	To FDA	Submission of the following promotional items for review: E-mail Campaign-American Journal of Managed Care, Application & Rotation Video 1, Application & Rotation Video 2, Application & Rotation DVD Cover & Label, Tabletop Display Panel, Promotional Slide Deck, Phoenix Trigger Letter-Savings Card Program, Phoenix Trigger Letter #1 – Email version, Days of the Week Convention Panel (multiple sizes), Days of the Week Convention Panel w/ Full Safety, Dosage Strength Convention Panel, Journal Ad Side by Side Convention Panels, Journal Ad Convention Panel and Header for Convention Booth, Torso Mannequin for Convention Booths, Tabbed FPI for Convention Touchscreen Kiosks, Touchscreen Version of the Butrans Initiation & Titration Guide, Touchscreen version of Butrans Patient Brochure, AMDA Product Theater Butrans Thank You letter, AMDA Butrans PT Program Ad Outsert, AMDA Butrans Product Theater Printed Poster, APhA Butrans Product Theater Welcome Letter, AAPM Product Theater Butrans Thank you Letter	PURCHI-003242369
Butrans	5/31/2011	To FDA	Submission of the following promotional items for review: Butrans REMS Website Meta Tags, Butrans Notimated Speaker Letter, Butrans Now Available eMail #2, Butrans savings card registration error page, Butrans Branded FPI, Butrans Large Type FPI, Spanish Medication Guide, Spanish Branded Large-type FPI, Spanish FPI, Butrans.com HCP pages	PURCHI-003242919
Butrans	2/3/2012	To FDA	Submission of the following promotional items for review: Fact Sheet, ACNP Product Theater Welcome Letter Packet, AAPM&R Product Theater Thank You Letter, Butrans Rep Delivered Invite e-Detail, Butrans Rep Invite to Portal, Product Information Kit, Butrans.com HCP pages, Butrans Rep delivered invite In-service, Fingertip Formulary Template	PURCHI-003245343
Butrans	5/14/2012	To FDA	Submission of the following promotional items for review: Experience Program Letters – Infomedics, RM Email Invitation_eDetail, RM Email Invitation-Portal (Discover), Experience Program – Infomedics Sample Report, Opioid Experienced Phoenix Trigger Email, RM Email Invitation_Inservice (ENGAGE), Updated	PURCHI-003245801

			Fingertip Formulary Templates, Packaging – Demo Samples, Journal of Pain and Symptom Management Reprint, INITIATIONS Retained Reference Guide, Tabletop Display Fabric Panel – Journal Ad Version, Rep invite to portal, Special Report-Third Installment (Opioid Experienced), Rep invite to INITIATIONS, Rep delivered invite In-services, Rep delivered invite e-Detail, Patient Savings Program – Pharm Sheet, Journal of Pain Reprint, Patient savings program and McKesson card, Fingertip Formulary pages, Fact Sheet, Promotional Slide Deck, Infomedics Patient savings program stickers	
Butrans	8/22/2012	To FDA	Submission of the following promotional items for review: SEM July Campaign, Branded FPI – Spanish, Butrans Card On Demand Letter, NADONA Product Theater Welcome Letter, Doctor’s Channel- DEA Requirement Script, Doctor’s Channel – Application Use, Shipping Letter, NADONA Product Theater Printed Poster, NADONA Product Theater ePoster, 2012 IVR for Patient Savings Program, Instructions for Use Tear Pad, Butrans Update to PurdueHCP.com, PTN Healthcasts Video Script, PTN Healthcasts Program Announcement, Purdue REMS Statement_070912, Purdue REMS Statement_070912 Internet, AOA Product Theater Program Book Description, NADONA Product Theater Thank You Letter, PainWeek Product Theater Program Book Description, ESI Formulary Announcement, AAFP Product Theater Invitation/Room Drop, PainWeek Product Theater ePoster, AOA Product Theater Invitation/Room Drop, PainWeek Product Theater Invitation/Room Drop, Doctor’s Channel-Dosing and Titration Script	PURCHI-003246730
Butrans	9/27/2012	To FDA	During the 3/31/2011 call with the FDA, Purdue suggested conducting market research about use of the term “single-entity.” In this submission, Purdue sent the FDA a report by Addison Whitney Health titled “Single Entity Opioid Comprehension Research: White Paper.”	PPLP004168571
Butrans	10/10/2012	To FDA	Submission of the following promotional items for review: PainWeek Product Theater Thank You Letter, PainWeek Product Theater Welcome Letter, Print Savings Card from Website Flashcard, PainWeek Product Theater Printed Poster, Wholesaler Sell Sheet, Promotional Slide Deck, PTN Healthcasts	PURCHI-003247026

			Survey Questions, Butrans.com MA Savings Card Language Removal, FPI Overview Presentation, AAFP Product Theater Program Book Description, Epocrates Formulary Flash Template, Butrans RM Email Invitation_eDetail, AOA Product Theater Invitation/Room Drop, Supplemental Analgesia and Titrations Brochure, Medco Formulary Win Email, Butrans IVR – Spanish – Patient Savings Program, AOA Product Theater ePoster, REMS Website	
Butrans	11/14/2012	To FDA	Submission of the following promotional items for review: Federal Pricing List, Shipping Letter, Hospice Letters Exhibits A&C, Hospice Rebate Summary, Nominated Speaker Letter, PurduePharma.com Products Section Update, P-Kinect Interactive Media, PurdueHCP.com, REMS Packet, Virginia Mason “No See” Email Letter	PURCHI-003248105
Butrans	12/18/2012	From FDA	FDA’s response to the 9/27/2012 white paper submission. <ul style="list-style-type: none"> “...we are not convinced that the findings suggest physician confusion surrounding the term ‘single-entity.’ Specifically, the results of the report indicate that the majority of physicians comprehend the term, ‘single-entity opioid’ without the claim, ‘Butrans does not contain APAP, an NSAID, or a COX-II inhibitor’...we maintain our position and recommend that you delete this claim. We remind you that we would not object to the use the claims, ‘single entity’ or ‘Only active ingredient.’” 	PPLP004168604
Butrans	1/3/2013	To FDA	Submission of the following promotional items for review: PainWeek Product Theater Thank You Letter, PainWeek Product Theater Welcome Letter, Print Savings Card from Website Flashcard, PainWeek Product Theater Printed Poster, Wholesaler Sell Sheet, Promotional Slide Deck, PTN Healthcasts Survey Questions, Butrans.com MA Savings Card Language Removal, FPI Overview Presentation, AAFP Product Theater Program Book Description, Epocrates Formulary Flash Template, Butrans RM Email Invitation_eDetail, AOA Product Theater Invitation/Room Drop, Supplemental Analgesia and Titrations Brochure, Medco Formulary Win Email, IVR-Spanish-Patient Savings Program, AOA Product Theater ePoster, REMS Website,	PURCHI-000531323

Butrans	1/17/2013	To FDA	Submission of the following promotional items for review: Speaker Programs – Promotional Slide Deck New Label – Animated, Hospice Letter Updated FPIs 2012, Tabletop Display Fabric Panel, Initiation Titration Guide, Patient Profile 2 – Nancy, Patient Profile 1 – Scott, Butrans.com website with Label Updates, Journal Ad Digital Size, Supplemental Analgesia Brochure, Decision Tree, Rep Delivered Invite eDetail, Recruitment eDetail eMail Series (Group DCA), Rep Invite to In-Service, Patients Savings Program Correspondence, Updated Templates, Opioid Naïve Clinical Trial Backgrounder, 2013 Patient Savings Program IVR, Core Sales Aid	PURCHI-003249187
Butrans	2/22/2013	To FDA	Submission of the following promotional items for review: Corporate Summary Brochure, Our Products Brochure, Phoenix Appointment Request Email, REMS Package Updates, Price Schedule Update, Hospice Letter w/ Updated FPIs, Email Unsubscribe Center, 2013 Federal Supply Schedule Price List	PKY183127706
Butrans	3/13/2013	To FDA	Submission of the following promotional items for review: Butrans.com Savings Card/Trial Offer Site Pages, 2013 Patient Savings Program IVR	PURCHI-003250339
Butrans	3/27/2013	To FDA	Submission of the following promotional items for review: www.purduerems.com	PKY183128025
Butrans OxyContin	4/10/2013	To FDA	Submission of the following promotional items for review: Genuine Product Identification Guide, PurdueHCP.com home page redesign, OxyContin, Butrans, and Intermezzo, Butrans/OxyContin Virginal Mason 'No See' Email Letter	PKY183128472
Butrans	5/7/2013	To FDA	Submission of the following promotional items for review: Initiations 1.0: Label Updates, Web Version, Clinical Reference Kit, APS Product Theater Room Drop Invite, Volunteer Speaker Recruitment Letter, Butrans Mobile Site	PURCHI-003252102
Butrans OxyContin	5/24/2013	To FDA	Submission of the following promotional items for review: P-Kinect Interactive Media – Butrans, OxyContin, OTC, Genuine Product Identification Guide – CBP version	PKY183129029
Butrans	7/1/2013	To FDA	Submission of the following promotional items for review: www.purduepharma.com, Hospice Rebate Program – Summary Sheet, Hospice Rebate Program – Exhibits A-C, May 3, 2013 PR Wholesaler Price Schedule	PKY183129652
Butrans	8/15/2013	To FDA	Submission of the following promotional items for review: Butrans.com website Redesign	PURCHI-003254847

Butrans	8/20/2013	To FDA	Submission of the following promotional items for review: New content to Patient Savings Programs on purduepharma.com	PKY183129909
Butrans	9/13/2013	To FDA	Submission of the following promotional items for review: 10/2/13 Price Schedule	PKY183130140
Butrans OxyContin	9/27/2013	To FDA	Submission of the following promotional items for review: 15 mcg/hour Convention Panel, 15 mcg/hour Decision Tree, 15 mcg/hour Patient Profile – Kathy, 15 mcg/hour Flashcard, 15 mcg/hour Initiation & Titration Guide, Focused Issue Brochure: Patient Access, Journal Ad: King Size, 15 mcg/hour Patient Brochure, Patient (Information Guide) Brochure for Website Use, Nominated Speaker Letter, Journal Ad: Digest, Conversion Tool on Butrans.com, 15 mcg/hour Announcement eMail, OxyContin & Butrans Nominated Speaker Letter	PURCHI-003256695
Butrans	9/27/2013	To FDA	Submission of the following promotional items for review: Product Identification Guide, Product Identification Guide – CBP Version	PKY183130413
Butrans	11/13/2013	To FDA	Submission of the following promotional items for review: Butrans.com 15 mcg/hr dose updates, Tabletop Display, 15 mcg/hr Pharmacy Sell Sheet Direct Mail, PainWeek Product Theater Thank You Letter, Mailer 15 15 mcg/hr and Business Reply Card, Paid Search Campaign, Banner Ads: IAB Standard, 15 mcg/hr eMail to Pharmacists	PURCHI-003258220
Butrans	11/18/2013	To FDA	Submission of the following promotional items for review: Purdue REMS Website	PKY183130753
Butrans	11/26/2013	To FDA	Submission of the following promotional items for review: LDM Group/Physician Care Emr Network Banner Ad, Rep Triggered eMail: 15 mcg/hour dosage strength, Experience Program – Holder and Kit Components – BUP073, Conversion Tool eMail, National Account Managers Presentation Deck, Formulary Announcement Grid, Formulary Grid, Nurse Educators Presentation Deck, Account Executive Presentation Deck	PURCHI-003258602

DDMAC Comments

ENDO			
Product	Date	Contents	Bates
Percocet	6/23/1999	<p>DDMAC Comments on Promotional Materials - a one page pharmacy journal advertisement, a physician journal advertisement, and a brochure with references:</p> <p><u>“Fair Balance</u> The brochure and physician's journal advertisement fail to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. . . . We suggest presenting this balancing information as additional bulleted points in a manner comparable to the claims for Percocet.”</p> <p><u>“Tried and True</u> In the brochure, you claim that Percocet is still the most recognized, trusted name in pain relief. DDMAC would consider this claim to be misleading without adequate evidence. We also remind you that there are non-prescription pain relievers that are widely promoted. We suggest that you revise this claim.”</p> <p><u>“Rapid Onset of Action</u> In the brochure, you claim that Percocet has a rapid onset of action (15-30 minutes). DDMAC would consider this claim of effectiveness to be misleading without substantial evidence. . . . [W]e suggest that you delete this claim.”</p> <p><u>“Little Risk of NSAID-like Side Effects</u> In the brochure, you claim that there is little risk of NSAID-like side effects. DDMAC would consider this claim of superiority over non -steroidal anti-inflammatory drugs to be misleading without substantial evidence. . . . Thus, . . . we suggest that you delete this claim.”</p> <p><u>“Powerful</u> DDMAC would consider the word ‘powerful’ [in the pharmacy journal advertisement] to be a claim of effectiveness for Percocet. Thus, the advertisement would require fair balancing information and would need to be accompanied by a ‘brief summary.’”</p>	ENDO-OPIOID_MDL-04640425

Percocet	8/19/1999	<p>DDMAC Comments on Promotional Materials - slim jim brochure, a pharmacy journal advertisement, and a physician journal advertisement:</p> <p>DDMAC comments should be applied to all current and future promotional materials for Percocet.</p> <p><u>“Slim Jim Brochure</u> <u>Unsubstantiated Claims</u></p> <ul style="list-style-type: none"> • The brochure presents the bolded phrase, ‘TRIED and TRUE,’ followed by the statement, ‘Still the most recognized, trusted name in oxycodone pain relief.’ . . . However, th[e] information [cited to support this claim] simply illustrates that Percocet is the most prescribed oxycodone preparation and is insufficient to support the claim that Percocet is ‘Still the most recognized, <u>trusted name</u> in oxycodone pain relief.’ (emphasis added).” <p><u>“Risk Information</u></p> <ul style="list-style-type: none"> • Page 11 and 12 of the slim jim brochure presents claims and information about Percocet dosing. Specifically, page 12 lists instances when ‘recommended dosage may be exceeded.’ Upon further review, this statement does not accurately convey the message, ‘It <u>may occasionally</u> be necessary to exceed the <u>usual</u> dosage....’ (emphasis added), as it is stated in the approved product labeling.” <p><u>“Pharmacy Journal Ad</u></p> <ul style="list-style-type: none"> • Endo has deleted the claim of ‘Powerful New Look’ and replaced it with the claim ‘Rolls in.’ . . . Although ‘Rolls in’ makes no claim about the drug's effectiveness, DDMAC would consider this claim to make a representation about the drug. Therefore, this advertisement would not be a reminder advertisement and would require a ‘brief summary.’” 	ENDO-OPIOID_MDL-04640997
Percocet	10/11/2001	<p>DDMAC Comments on the Proposed Promotional Materials for Percocet – two-sided sales aid and journal advertisement:</p> <p><u>“Sales Aid</u> <u>Misleading Claims</u></p> <p>Your promotional pieces present pictorials of people windsurfing and scuba diving. Your pictorials suggest that Percocet therapy will result in pain relief that allows patients to perform rigorous activities such as wind surfing or scuba diving. . . . However, this outcome is not representative of the typical response that a patient can expect with Percocet therapy. Therefore, your pictorials are misleading. Furthermore, your pictorials are also misleading because they minimize the risk that</p>	ENDO-OPIOID_MDL-05408804

		<p>‘Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET should be cautioned accordingly.’ as stated in the approved product labeling (PI).”</p> <p>“You present the claims ‘Less acetaminophen. More Flexibility.’ and ‘Reformulated to provide effective pain management with lower levels of acetaminophen.’ These claims imply that the new dosage forms of Percocet contain less acetaminophen than other Percocet dosage forms. However, the new dosage forms contain the same amount of acetaminophen as Percocet 2.5 mg/325 mg and 5 mg/325 mg. Therefore, we recommend that you revise these claims.”</p> <p>“[T]he tagline ‘Less acetaminophen. More flexibility’ implies that because there is ‘less acetaminophen’ these products offer more dosing flexibility. However, according to the PI, the maximum recommended daily doses of Percocet 7.5 mg/325 mg and Percocet 7.5 mg/500 mg are identical. In addition, the maximum recommended daily doses of Percocet 10 mg/325 mg and Percocet 10 mg/650 mg are identical. Therefore, your tagline is misleading because the new dosage forms do not offer greater dosing flexibility than other available strengths of Percocet.”</p> <p>“The claim ‘one tablet every 6 hours for effective pain relief’ and the picture of a prescription imply that the product should be scheduled every 6 hours. However, the PI states, ‘The usual adult dosage is one tablet every 6 hours as needed for pain (emphasis added).’”</p> <p>Journal Ad <u>Fair Balance</u> “The efficacy information is presented throughout the journal ad as large headlines and claims in large bold type. In contrast, the contraindications and adverse reactions appear at the bottom of the journal ad in small, less prominent type that is difficult to read. Therefore, we object to the presentation of risk information in this journal ad taking into account all implementing factors used to achieve emphasis such as layout, headlines, and contrast.”</p>	
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Percocet	11/26/2001	DDMAC Comments on the Proposed Promotional Materials for Percocet Revised in Response to DDMAC 10/11/2001 Letter: “As discussed in a teleconference on October 15, 2001, DDMAC has reviewed the revised proposed promotional materials and does not have any comments at this time.”	ENDO-OPIOID_MDL-05408921
OPANA ER and OPANA	7/12/2006	DDMAC Comments on OPANA Logo: “[T]he term ‘New’ should only be used for six months from the time a product is initially marketed.”	END00036670
OPANA ER and OPANA	8/4/2006	DDMAC Comments on Promotional Materials - Dosing Detail Aid for OPANA ER and OPANA: Omission of Material Facts “Page 1 of the proposed Dosing Detail Aid presents a partial indication for Opana ER and omits the following from the Indications and Usage section of the Opana ER PI: ‘OPANA ER is not indicated for pain in the immediate post-operative period (12 -24 hours following surgery) for patients not previously taking opioids because of the risk of oversedation and respiratory depression requiring reversal with opioid antagonists.’” “[P]age 3 of the proposed Dosing Detail Aid includes the statement. ‘OPANA ER TABLETS are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed OPANA ER TABLETS leads to the rapid release and absorption of a potentially fatal dose of oxymorphone’ (original emphasis). However, the following is omitted from the Dosage and Administration section of the Opana ER PI: ‘Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone’ (original emphasis).” “[P]age 4 of the proposed Dosing Detail Aid presents some Contraindications from the Opana ER PI, but omits the following remaining Contraindications: ‘OPANA ER is not indicated for pain in the immediate post-operative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OPANA ER is only	ENO000026959

indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate or severe and persist for an extended period of time.”

Minimization of Risk

“[T]he proposed Dosing Detail Aid uses large and colorful headers and a chart to highlight the efficacy and dosage and administration of Opana ER and Opana, while the indications and risk information are presented without comparable emphasis in single-spaced format.”

“Pages 1 and 4 of the proposed Dosing Detail Aid discuss the abuse liability of Opana ER and Opana. These presentations are misleading because they minimize the risks associated with Opana ER and Opana and suggest the drug products are safer than has been demonstrated. According to the Warnings - Misuse, Abuse and Diversion of Opioids section of the Opana ER PI, ‘Opioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. OPANA ER tablets may be abused by crushing, chewing, snorting or injecting the product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **WARNINGS: Drug Abuse and Addiction**).’” Furthermore, the Warnings Drug Abuse and Addiction. Controlled Substance section of the Opana ER PI states. ‘Abuse of OPANA ER poses a risk of overdose and death. This risk is increased with concurrent abuse of OPANA ER with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV. . . . Moreover, the Safety and Handling section of the Opana ER PI states, ‘OPANA ER contains oxymorphone, which is a controlled substance. Oxymorphone is controlled under Schedule II of the Controlled Substances Act. Oxymorphone, like all opioids, is liable to diversion and misuse and should be handled accordingly. Patients and their families should be instructed to flush any OPANA ER tablets that are no longer needed.’” (alteration marks omitted).

DDMAC then noted that similar warnings exist in the Opana PI and “recommend[ed] [Endo] include this information for consistency with Opana ER and Opana

		<p>PIs.”</p> <p>Lack of Contextual Information</p> <p>“Page 3 of the proposed Dosing Detail Aid discusses initiating OPANA therapy in opioid-naïve patients This presentation is misleading because it lacks important contextual information” from the Opana PI that “The dose should be titrated based upon the individual patient's response to their initial dose of Opana. This dose can then be adjusted to an acceptable level of analgesia taking into account the pain intensity and side effects experienced by the patient.””</p> <p>“Page 3 of the proposed Dosing Detail Aid also contains the statements, ‘Conversion from other opioids’ (original emphasis). This presentation is misleading because it lacks important contextual information from the Dosage and Administration section of the Opana ER and Opana PIs, ‘Conversion from Other Oral Opioids’ (emphasis added).”</p> <p>In general, it is safest to start the OPANA therapy by administering half of the calculated total daily dose of OPANA ER (see conversion ratio table below) in 2 divided doses, every 12 hours. The initial dose of OPANA ER can be gradually adjusted until adequate pain relief and acceptable side effects have been achieved.</p> <p>Due to patient variability with regard to opioid analgesic response upon conversion, patients should be closely monitored to ensure adequate analgesia and to minimize side effects." We recommend you include this important contextual information for consistency with both the Opana ER PI and the Opana PI.</p> <p>Page 4 of the proposed Dosing Detail Aid states, "The most common adverse drug reactions (>10%) in clinical trials for OPANA ER were... dizziness..." This presentation is misleading because it lacks important contextual information. According to the Adverse Reactions section of the Opana ER PI, "The most common adverse drug reactions (>10%) reported at least once by patients treated with OPANA ER in the clinical trials were... dizziness (ex. vertigo)..." (second emphasis added).</p> <p>Overstatement of Efficacy/Broadening of Indication</p> <p>“Page 1 of the proposed Dosing Detail Aid includes claims such as, ‘From hospital to home, effectively</p>	
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		address your patients' moderate to severe pain across the continuum of care ... STAY AHEAD OF PAIN' (original emphasis) and page 2 contains the headline claim, 'From hospital to home, effectively address your patients' moderate to severe pain across the continuum of care.' These claims are misleading because they overstate the efficacy of Opana ER and Opana therapy by implying that patients will have guaranteed prophylaxis and effectiveness against pain, when such has not been demonstrated by substantial evidence. In addition, these claims are misleading because they imply that Opana ER and Opana are useful in a broader range of conditions or patients than has been demonstrated by substantial evidence, and suggest that the drugs may be used in all patients with moderate to severe pain in all home and hospital settings."	
OPANA ER	4/30/2012	<p>DDMAC Response to OPANA ER TRF Professional Detail Aid:</p> <p>"General DPDP reminds you that terms such as 'new' and 'introducing' should only be used for six months after the date Opana ER is initially marketed."</p> <p>Minimization of Risk Information/Implied Unsubstantiated Safety Superiority Claims</p> <p>"The proposed detail aid contains numerous claims and presentations describing Opana ER's new formulation and its INTAC™ technology. For example, page two includes claims such as the following (bolded emphasis original; underlined emphasis added):</p> <ul style="list-style-type: none"> • 'INTAC™ technology provides mechanical stability' • 'Innovative manufacturing process uses heat extrusion to <u>create mechanical strength</u>' • 'New formulation of Opana® ER tablets with INTAC technology <u>has the mechanical strength to provide an obstacle to crushing by tools, including hammers, spoons, and mechanical pill crushers</u>' <p>Additionally, page three includes claims and presentations such as the following regarding a blinded comparative study in 25 subjects (bolded emphasis original):</p> <ul style="list-style-type: none"> • 'Opana® ER with INTAC™ technology compared to oxymorphone ER (original formulation). . . Provided some resistance to crushing by tools, including spoons, a hammer, or a razor' 	ENDO-CHI_LIT-00270449

- ‘**Manipulating Opana® ER tablets with INTAC™ technology resulted in larger particle size than oxymorphone ER (original formulation)**’ (with accompanying visual)
- ‘**Study demonstrated the difficulty in forming an intranasal preparation**’ (with accompanying visuals)

The totality of these claims and presentations suggest that, as a result of its new formulation, Opana ER offers a therapeutic advantage over the original formulation when this has not been demonstrated by substantial evidence or substantial clinical experience. In addition, these claims misleadingly minimize the risks associated with Opana ER by suggesting that the new formulation’s ‘INTAC™ technology’ confers some form of abuse deterrence properties when this has not been demonstrated by substantial evidence.”

Omissions of Material Facts

“Page one of the proposed detail aid presents information from the Indications and Usage section of the PI. This presentation is misleading because it omits the following information from the Indications and Usage section of the full PI: . . . OPANA ER is only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate or severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate.”

“[T]he proposed detail aid omits the following important risk information from the PI (in pertinent part) (bolded emphasis original; underlined emphasis added):

5.2 Respiratory Depression

...

Administer OPANA ER with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma.

5.3 Misuse, Abuse and Diversion of Opioids

...

Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion

		<p>...</p> <p><u>OPANA ER tablets may be abused by crushing, chewing, snorting, or injecting the product. These practices will result in the less controlled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death</u></p> <p>...</p> <p><u>Healthcare professionals should advise patients to store OPANA ER in a secure place, preferably locked and out of the reach of children and other non-caregivers."</u></p>	
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Warning Letter

JANSSEN			
Product	Date	Contents	BATES
Duragesic	9/2/2004	<ul style="list-style-type: none"> • False or misleading safety claims <ul style="list-style-type: none"> ○ Low reported rate of mentions in DAWN (Drug Abuse Warning Network) data, with data comparing it to other opioids <ul style="list-style-type: none"> ▪ DAWN data can't provide valid comparison—not clinical trial data but surveillance system ▪ Duragesic not as widely prescribed so could be lower frequency of use not lower incidence ○ Minimizes potential for local GI side effects by avoiding GI absorption with table showing constipations rates <ul style="list-style-type: none"> ▪ Suggests lower than other opioids, not substantiated • Unsubstantiated effectiveness claims <ul style="list-style-type: none"> ○ <i>Demonstrated effectiveness in chronic back pain</i> <ul style="list-style-type: none"> ▪ Based on Simpson study—inadequate as open label single arm w/ no control group ○ <i>86% of pts experienced overall benefit in clinical study based on pain control, disability in ADLs, qualify of sleep</i> <ul style="list-style-type: none"> ▪ Based on same study ○ <i>Long terms effects—12 month open label shows significant improvement in physical functioning score, social functioning</i> <ul style="list-style-type: none"> ▪ Based on uncontrolled Milligan study—not adequate in design ○ <i>Improved patient outcomes shown in open label crossover study compared to sustained release oral morphine</i> <ul style="list-style-type: none"> ▪ Allen study can't minimize bias in reporting of subjective responses in a general healthcare questionnaire ○ <i>1360 loaves and counting....work/life uninterrupted...think less about pain...supports functionality</i> <ul style="list-style-type: none"> ▪ Unsubstantiated 	JAN-MS-00779345
Duragesic	9/30/2004	<p>DDMAC response regarding submission of promotional file card and change in position.</p> <p><u>Broadening of indication:</u></p>	JAN-MS-0023891

		<ul style="list-style-type: none"> • 'Up to 72 hours of uninterrupted pain relief per patch.' This claim implies that Duragesic is appropriate for patients with all types of pain and for any duration or under any circumstances, when this is not the case." • "...your promotional piece is misleading because it suggests that Duragesic is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence" <p><u>Suggestions</u></p> <ul style="list-style-type: none"> • "...we suggest that you prominently present Duragesic's indication with its limitations contiguously (including the statement "Duragesic should not be used in the management of acute or postoperative pain because serious or life-threatening hypoventilation could result") before, or in conjunction with your initial claims of efficacy for Duragesic." • "we...suggest that you prominently present the indication and limitations to use with your efficacy claims throughout your promotional piece.." <p><u>Minimization and Omission of Risk Information</u></p> <ul style="list-style-type: none"> • Content: "numerous efficacy claims for Duragesic" but failure to "present important risk information: • Presentation "claim that Duragesic has a "favorable side-effect profile" is misleading because it minimizes these serious and important risks <p><u>Suggestions</u></p> <ul style="list-style-type: none"> • "...we suggest that you prominently present risk information for Duragesic throughout your promotional file card." • "suggest that you more prominently present the claim 'Please see important safety information, including Boxed Warning, on pages...'" 	
Duragesic	12/28/2004	<p>Response letter to proposed Dear Healthcare provider submission dated October 15, 2004</p> <ul style="list-style-type: none"> • Proposed revisions including prominently cite studies referred to in letter 	JAN-MS-00238397

Company Response to Warning Letter

JANSSEN			
Product	Date	Contents	BATES
Duragesic		Janssen response to DDMAC letter dated September 2, 20004	JAN-MS-

	9/17/2004	<ul style="list-style-type: none"> Janssen disagrees “with DDMAC's position that the professional file card (DR-850) for Duragesic makes false or misleading statements about the abuse potential, effectiveness and other risks of the drug. Janssen and J&J PRD also respectfully disagree with DDMAC that by suggesting that Duragesic has a low potential for abuse compared to other opioid products the file card encourages the unsafe use of the drug in such a way that could potentially result in serious or life-threatening hypoventilation. <p><u>Low Abuse potential</u></p> <ul style="list-style-type: none"> Janssen cites following sources of information to support low abuse claim: Zacny of al (2003), Joranson et al (2000), Coleman et al (Manuscript) <p><u>Tagline</u></p> <ul style="list-style-type: none"> Claim tagline “Life, Uninterrupted” is it is “not intended to represent any quality of life claims.” <p><u>Plan of Action</u></p> <ul style="list-style-type: none"> Discontinue professional file card Discontinue all promotional material containing same or similar representations Development of promotion aid for representatives to use with HCPs that received promotional material 	00238384
Duragesic	10/15/2004	Letter from Janssen submitting draft of Dear Healthcare Professional letter notifying HCPs of Janssen’s receipt of warning letter	JAN-MS-00291336_
Duragesic	1/13/2005	Letter from Janssen submitting revised draft Dear Healthcare Professional letter.	JAN-MS-00291340

Notice of Violation Letters

JANSSEN			
Product	Date	Contents	BATES
Duragesic	3/5/1998	<ul style="list-style-type: none"> • Misleading comparisons to competitive agents <ul style="list-style-type: none"> ○ <i>Duragesic provides less frequency and impact of side effects.</i> ○ Implies less constipation than other opioids • Promotion of Unapproved Use <ul style="list-style-type: none"> ○ Broadening of indication not supported by substantial evidence for <i>Chronic Pain</i> ○ Implies can be used for any kind of pain, rather than for pain that cannot be managed by lesser means ○ Janssen to be promoting Duragesic for a much broader use than that recommended in the approved product labeling. • Unsubstantiated claims/False or Misleading Statements <ul style="list-style-type: none"> a. <ul style="list-style-type: none"> ○ <i>Duragesic provides less frequency and impact of side effects.</i> ○ Implies less constipation than other opioids ○ Suggestions that the use of Duragesic is not associated with constipation are false or misleading. b. "[s]tops the pain. Not the patient," <ul style="list-style-type: none"> ○ Implies that use is not associated with impairment which is false and misleading • Lack of fair balance—must present info relating to warnings & side effects with prominence and readability reasonably comparable to presentation of info re effectiveness <ul style="list-style-type: none"> ○ Numerous efficacy & safety claims w/o any risk info • Misrepresentation of safety info <ul style="list-style-type: none"> ○ <i>Duragesic provides less frequency and impact of side effects.</i> ○ Unsubstantiated superiority claim ○ Minimizes risk of constipation 	JAN-MS-03090752
Duragesic	4/16/1998	<p>Response to Janssen's letter dated March 18, 1998</p> <p><u>Less Constipation Claim</u></p> <ul style="list-style-type: none"> • Ten articles submitted by Janssen to support claim that Duragesic causes significantly less constipation than oral morphine have "serious flaws in the study design" and thus "cannot be relied upon for showing comparative differences between Duragesic and oral morphine in relation to the incidence of constipation associated with the use of each drug." 	JAN-MS-03090859

		<ul style="list-style-type: none"> “...proposed presentation of the results of the Ahmedzai and Brooks study comparing the efficacy of response and the incidence of constipation associated with the use of Duragesic and oral morphine would be considered false or misleading.” <p><u>For Chronic Pain claim</u></p> <ul style="list-style-type: none"> “DDMAC would object to this proposal because the broad indication at the top of the poster still overpowers the approved indication presented at the bottom of the poster. Untrue or misleading information in any part of a promotion cannot be corrected by the inclusion in another distinct part of the promotion of a brief statement containing true information. <p><u>False or Misleading Statements – “Stops the Pain. Not the Patient”</u></p> <ul style="list-style-type: none"> “Janssen submitted no data to substantiate such quality of life claims.” 	
Duragesic	2/15/2000	DDMAC Letter to Janssen regarding the dissemination of “homemade” promotional pieces by Janssen representatives to physicians in Georgia and Florida	Not Produced; See JAN-MS-00901267
Duragesic	3/30/2000	DDMAC letter to Janssen regarding the dissemination of “homemade” promotional pieces. <ul style="list-style-type: none"> Misrepresenting of superiority on safety <ul style="list-style-type: none"> <i>Significantly LESS constipation!</i> Implies than other opioids Broadening of indication not supported by substantial evidence <ul style="list-style-type: none"> <i>It’s not just for end stage cancer anymore!</i> Implies can be used for any kind of pain, which contradicts BB warning that it is not for acute or post op pain Unsubstantiated claims <ol style="list-style-type: none"> <i>Preferred regimen: 2x per week versus 2x per day!</i> <ul style="list-style-type: none"> Suggests preferable to oral opioids taken 2x day <i>Easy for Patient Compliance</i> <ul style="list-style-type: none"> Suggests compared to other opioids <i>#1 reason to convert: QUALITY OF LIFE—w/p pain, pts sleep better, increase daily activities, spend more qualify time with families</i> <ul style="list-style-type: none"> Health-related QOL claims require SSE in form of adequate & well controlled studies designed to specifically address these outcomes Lack of fair balance—must present info relating to warnings & side effects with prominence and readability reasonably comparable to presentation of info re 	JAN-MS-00238338

		<p>effectiveness</p> <ul style="list-style-type: none"> ○ Numerous efficacy & safety claims w/o any risk info • Misrepresentation of safety info <ul style="list-style-type: none"> ○ <i>Results in <i>much less Constipation</i> compared to Oxy</i> ○ Unsubstantiated superiority claim ○ Minimizes risk of constipation <p>Failure to submit promo materials at time of initial dissemination</p>	
Duragesic	5/1/2000	Letter from DDMAC to Janssen finding it's action in response to notice regarding "homemade" promotional pieces to be acceptable.	JAN-MS-02580546

Company Responses to Notice of Violation Letters

JANSSEN			
Product	Date	Contents	BATES
Duragesic	3/18/1998	<p>Janssen Response to March 5, 1998 DDMAC letter</p> <p><u>Misleading Comparisons to Competitive Agents</u></p> <ul style="list-style-type: none"> • "...the overall finding (Duragesic is associated with less constipation than morphine) is well reported in the literature." <p><u>Promotion of Unapproved Use</u></p> <ul style="list-style-type: none"> • "'We acknowledge that the approved indication is for "the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means...'. " <p><u>False or Misleading Statements</u></p> <ul style="list-style-type: none"> • "Janssen disagrees that the use of the phrase "Stops the pain. Not the patient," indicates or implies that Duragesic is not associated with impairment of mental or physical abilities. The intended message to be conveyed by this statement is that the use of Duragesic enables patients to lead more normal lives, a theme which has been consistently used in Duragesic promotion and advertising since the launch of the product in 1991." <p><u>Fair Balance</u></p> <ul style="list-style-type: none"> • Janssen reports promotional material that has been discontinued due to not prominently including risk information 	JAN-MS-03090755
Duragesic	4/8/1998	<p>Letter from Janssen to DDMAC</p> <p>Janssen agreed to modify convention posters:</p> <ul style="list-style-type: none"> • "headline 'For Chronic Pain' has been linked to the full indication" • "listing of the most common adverse events associated 	JAN-MS-03090852

		<p>with the use of Duragesic has been added”</p> <ul style="list-style-type: none"> • “new quote has been selected for display” 	
Duragesic	2/29/2000	<p>Letter from Janssen to DDMAC regarding letter dated February 15, 2000 .</p> <ul style="list-style-type: none"> • 85 physicians in Georgia were mailed “homemade” promotional pieces • Single sales representative in Florida disseminated a “homemade” sales piece to a limited number of healthcare providers • “We are extremely concerned about this activity. Janssen has a strict policy regarding product promotion and use of, or dissemination of, any selling aids not approved by the home office is a clear violation of our internal policy.” 	JAN-MS-00901267
Duragesic	4/12/2000	<p>Janssen letter to DDMAC re “homemade” promotional pieces</p> <ul style="list-style-type: none"> • “Janssen did not sanction these pieces and we have taken corrective actions to prevent reoccurrence of this type of activity.” • “With the exception of the patient preference claim “Preferred regimen: 2 x per week versus 2 x per day!”, no currently Janssen sanctioned promotional pieces contain the same or similar claims or presentations as the homemade promotional pieces.” 	JAN-MS-03090751

DDMAC Discussions

JANSSEN			
Product	Date	Contents	BATES
Duragesic	5/10/2000	<p>Teleconference to discuss plans for Direct to Consumer (DTC) advertising</p> <ul style="list-style-type: none"> Janssen “reviewed the rationale for DTC, explaining the general growth in the pain treatment market and the recent data indicating a general under-treatment of pain.” “... DDMAC is not thrilled by the idea but there are no regulations preventing [Janssen] from moving forward”. 	JAN-MS-00479787
Duragesic	6/8/2000	<p>Duragesic DTC meeting request</p> <p>DDMAC discussed concerns with Janssen’s planned DTC campaign:</p> <ul style="list-style-type: none"> “current language regarding dependence is not strong enough” “concern about the patient population being targeted.” 	JAN-MS-00479784
Duragesic	9/15/2000	<p>Minutes of September 8, 2000 meeting</p> <p>Key Points:</p> <ul style="list-style-type: none"> FDA expressed concerns that DTC advertising could result in increased serious adverse events due to inappropriate use or use by inexperienced physicians. The print ad needs to include a clear link to the reason why Duragesic should not be used in opioid-naive patients. Additional revisions are needed to certain language in the print ad. 	JAN-MS-00479781
Duragesic	12/18/2000	<p>Call regarding DTC advertising campaign</p> <ul style="list-style-type: none"> Janssen “decided not to proceed with the Direct to Consumer advertising campaign at this time.” 	JAN-MS-00480543
Duragesic	1/4/2001	<p>DDMAC meeting to discuss Duragesic Effectiveness Trial and use of the trial results in a promotional claim for patient satisfaction versus OxyContin</p> <p>Meeting Highlights:</p> <ul style="list-style-type: none"> FDA sees pain relief (efficacy) as intertwined with patient satisfaction as satisfaction is dependent of pain relief. Therefore, patient satisfaction cannot be measured in an open-label trial. Due to the bias of an open-label design, there is no way to assess whether the drugs are being dosed comparably and if the difference in pain relief is due to the drug or to the way it is being dosed/prescribed. Results of the proposed study could be used descriptively in promotion but would need to include strong disclaimers, including statements that dosing was not comparable and that the study design was inadequate to measure efficacy. 	JAN-MS-00654881

Notice of Violation Letter

JANSSEN			
Product	Date	Contents	BATES
Nucynta IR	8/26/2011	<p>FDA sent Janssen a Notice-of-Violation Letter for oral statements made by an Ortho-McNeil-Janssen representative on December 18, 2010, at the 2010 American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting and Exhibition in Anaheim, CA, regarding its drug NUCYNTA® (tapentadol) immediate-release oral tablets C-II (Nucynta)."</p> <p>Claims:</p> <ul style="list-style-type: none"> • "Nucynta is useful in the treatment of Diabetic Peripheral Neuropathic Pain (DPNP)." • "DPNP patients stay on Nucynta for longer, and Nucynta provides 10 mg of opioid/oxycodone pain control, similar to tramadol, but with less GI, constipation, nausea, and vomiting." • Physicians "won't have to put patients on docusate or senna, patients get out of the hospital a day earlier which saves thousands of dollars because they are going to be able to have a bowel movement" <p>Violations: FDA considered the statements to promote an unapproved use for Nucynta, make unsubstantiated superiority and other claims about the drug, and minimize the serious risks associated with Nucynta.</p> <ol style="list-style-type: none"> 1. Promotion of Unapproved Use: "Nucynta is not approved by FDA for the treatment of DPNP, a chronic pain condition that would require a specific indication" 2. Unsubstantiated Superiority Claims/Minimization of Risk: Claims imply "Nucynta has been shown to have less GI (gastrointestinal) adverse reactions (i.e., constipation, nausea, and vomiting), in comparison to oxycodone and/or tramadol, when this is not the case...Furthermore, the sales representative's claim that Nucynta results in less constipation, nausea, and vomiting minimizes the risks associated with the use of Nucynta and suggests that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.... claim [regarding docusate] suggests that Nucynta-treated patients will have a bowel movement without the use of docusate or senna, which will result in a reduction in the length of hospital stay compared to oxycodone and tramadol. FDA is not aware of substantial evidence or substantial clinical experience to support such claims. 3. Unsubstantiated Efficacy Claim: "statement that Nucynta provides 10 mg of opioid/oxycodone pain control 	JAN-MS-02273742

		<p>similar to tramadol is misleading because it implies that Nucynta has been shown to be non-inferior to oxycodone, tramadol, or other opioids... FDA determined that your analyses to obtain a non-inferiority claim regarding the efficacy of Nucynta compared to oxycodone were inadequate... FDA is not aware of any well-controlled head-to-head clinical trials comparing the efficacy of Nucynta to tramadol or any other opioids.”</p> <p>FDA Conclusion and Requested Actions:</p> <ul style="list-style-type: none"> oral statements made by the Ortho-McNeil-Janssen representative misbrand Nucynta in violation of the Act, 21 U.S.C. 352(f)(1) & (n). Ortho-McNeil-Janssen immediately cease violative promotional activities for Nucynta such as those described above. 	
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Company Response to Notice of Violation Letter

JANSSEN			
Product	Date	Contents	BATES
Nucynta IR	9/12/2011	<p>Janssen’s response to the FDA’s Notice of Violation letter from 8/26/2011.</p> <p>Summary</p> <ul style="list-style-type: none"> Janssen is “not aware of promotional activities for NUCYNTA that contain statements/claims such as those describes in the notice of violation letter” “Following the conclusion of our internal investigation we will take corrective action as appropriate, up to and including dismissal of the representative.” 	JAN-MS-00230368

FDA 7/14/2004 Meeting Minutes

TEVA			
Product	Date	Contents	BATES
Actiq	7/14/2004	<p>On July 14, 2004, Cephalon employees met with the FDA to provide an update on information related to, among other things, abuse, diversion, misuse, overdose, death and off-label use of Actiq, and any non-compliance issues that Cephalon was aware of related to the risk management plan implementation of Actiq.</p> <p>Summary</p> <ul style="list-style-type: none"> • “Available data suggests considerable off-label use of Actiq and the Agency would like to understand the steps Cephalon is taking to discourage such use and ensure that off-label promotion is not occurring.” • “Physicians are not screened for whether they treat cancer patients.” • “Sales representatives also call upon physicians known to use Actiq, including physicians who prescribe it for off-label uses.” • The FDA sought clarification on several issues, including: <ul style="list-style-type: none"> ○ DDMAC expressed concerns about the information provided and in the background materials regarding the sponsor’s promotional practices as they relate to off-label use ○ Increasing distribution of Actiq Welcome Kits • A meeting with DDMAC was held August 30, 2004 	TEVA_MDL_A_01582360

Official DDMAC 8/30/2004 Meeting Minutes

TEVA			
Product	Date	Contents	BATES
Actiq	8/30/2004	<p>FDA Letter attaching final meeting minutes from 8/30/2004 DDMAC meeting.</p> <p>Summary</p> <ul style="list-style-type: none"> • Discussion points included DDMAC's concerns regarding: <ul style="list-style-type: none"> ○ Off-label use of Actiq ○ The targeting criteria and lack of screening for physicians called upon by Cephalon's sales force to promote Actiq ○ Training/detailing practices which inappropriately broaden the drug's labeled indication ○ The eliciting of and response to off-label inquiries regarding Actiq ○ Minimizing the fatal risk of Actiq to children ○ The promotional use of disease awareness materials that discuss conditions for which Actiq is not indicated to treat • "DDMAC expressed significant concerns about the increasing off-label use of Actiq" • "DDMAC expressed concerns that Cephalon's training and detailing practices appear to encourage the off-label use of Actiq rather than discourage it. • DDMAC was monitoring the promotion of Actiq "very closely" • "DDMAC also noted that FDA is prepared to take whatever action is necessary to address any violations and ensure that Cephalon complies with the law and that the public health is protected." • "Cephalon should also be aware that DDMAC has received complaints about its promotion, and that it is under scrutiny by others who are concerned about the potential for harm to the public health from inappropriate use of Actiq." 	TEVA_MDL_A_01584978

9/29/2004 DDMAC Promotional Material Letter

TEVA			
Product	Date	Contents	BATES
Actiq	9/29/2004	<p>Letter from DDMAC to Cephalon providing comments on proposed promotional materials for Actiq.</p> <p>Summary</p> <ul style="list-style-type: none"> • DDMAC provides comments on Actiq Patient Profiles • “Unsubstantiated Comparative Claims” <ul style="list-style-type: none"> ○ “You present multiple claims under the header, ‘Managing breakthrough pain,’ such as, ‘Prior treatment: Ibuprofen and Percocet’ and ‘Prior Treatment: MSIR’ in addition to claims that compare Actiq with ‘regular rescue medications.’ Such claim are misleading..” • “Lack of Important Contextual Information” <ul style="list-style-type: none"> ○ “These and similar claims are misleading because they imply that it is appropriate for patients to consume as many Actiq units as needed” • “Overstatement of Efficacy” 	TEVA_MDL_A_07424105

October 2004 DDMAC Promotional Material Letter

TEVA			
Product	Date	Contents	BATES
Actiq	10/2004	<p>Letter from DDMAC to Cephalon providing comments on proposed promotional materials for Actiq.</p> <p>Summary</p> <ul style="list-style-type: none"> • DDMAC provides comments on Actiq Spanish Warning Stickers, Actiq Montage Journal Ad, and Actiq Detail Aid. • “Misleading Presentation of Information” in Actiq Montage Journal Ad <ul style="list-style-type: none"> ○ “This claim is misleading because it implies that it is appropriate for patients to consume as many Actiq units as needed” • “Minimization of Risk” in Actiq Montage Journal Ad <ul style="list-style-type: none"> ○ “You present the claim, ‘The adverse events seen with Actiq are typical opioid side-effects...’ This claim is misleading because Actiq is the only opioid approved with a risk management plan, and there are several prominent boxed warnings related to safety that appear in the approved labeling and that are exclusive to Actiq.” • “Omission of Important Risk Information” in Actiq Detail Aid <ul style="list-style-type: none"> ○ “This detail aid is misleading because you fail to communicate any Prevention of Diversion and Abuse Messages.” 	TEVA_MDL_A_00267691

11/29/2005 DDMAC Promotional Material Letter

TEVA			
Product	Date	Contents	BATES
Actiq	11/29/2005	<p>Letter from DDMAC to Cephalon providing comments on proposed promotional materials for Actiq.</p> <p>Summary</p> <ul style="list-style-type: none">• DDMAC provides comments on proposed prescribing guide, including Pocket dosing guide, Booth panels, and a Journal ad.• “The totality of this presentation is misleading because it implies that Actiq is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence.”• “Overstatement of Efficacy” in Journal Ad<ul style="list-style-type: none">○ “These claims are misleading because they overstate the efficacy of Actiq and imply that Actiq is guaranteed to provide adequate and effective response and pain relief for every patient every time the product is used, when such is not the case.”• “Misleading Claim” in Journal Ad<ul style="list-style-type: none">○ “This claim is misleading because it implies that it is appropriate for patients to consume as many Actiq units as needed to control all episodes of breakthrough cancer pain per day, when such is not the case.”	TEVA_MDL_A_01583546

3/26/2009 DDMAC Letter re Misleading Sponsored Links

TEVA			
Product	Date	Contents	BATES
Fentora	3/26/2009	<p>Untitled Letter from DDMAC pertaining to Cephalon's sponsored links on internet search engines for Fentora.</p> <p>Summary</p> <ul style="list-style-type: none"> • "The sponsored links are misleading because they make representations and/or suggestions about the efficacy of Fentora and Treanda, but fail to communicate any risk information associated with the use of these drugs." • "In addition, the sponsored links for Fentora inadequately communicates the drug's indication." • "This omission of risk information is particularly concerning as one of the products, Fentora, has a Boxed Warning." • "Fentora is only indicated for the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. The misleading suggestion conveyed by the sponsored link that Fentora is appropriate for all cancer patients with breakthrough pain is especially concerning given that Fentora must not be used in opioid non-tolerant patients because life-threatening hypoventilation and death could occur at any dose in patients not on a chronic regimen of opioids." • "DDMAC requests that Cephalon immediately cease the dissemination of violative promotional materials for Fentora and Treanda." 	TEVA_MDL_A_06378822

4/27/2009 DDMAC Regulatory Contact Report

TEVA			
Product	Date	Contents	BATES
Fentora	4/27/2009	<p>Regulatory Telephone Contact Report addressing promotional materials for Fentora.</p> <p>Summary</p> <ul style="list-style-type: none">• “On March 26, 2009, Cephalon received an untitled letter from the Division of Drug Marketing, Advertising and Communications (DDMAC) of the US Food and Drug Administration (FDA) pertaining to DDMAC's review of Cephalon, Inc's (Cephalon) sponsored links on internet search engines (e.g., Google.com) for FENTORA (fentanyl buccal tablets) and TREANDA (bendamustine hydrochloride) for injection. The letter indicated that the sponsored links were misleading because they made representations and/or suggestions about the efficacy of FENTORA and TREANDA but failed to communicate any risk information associated with the use of these drugs.”• “DDMAC requested that Cephalon immediately cease the dissemination of violative promotional material for FENTORA and TREANDA, consistent with the points described above. DDMAC requested that Cephalon respond to their letter by April 9, 2009, indicating whether we intended to comply with their request, list all promotional materials in use for these drugs as of the date of their letter, identify which materials contained violations described above, and provide explanation of Cephalon's plan for discontinuing use of such materials.”• “On April 8, 2009, Cephalon provided written correspondence to DDMAC delineating the active TREANDA and FENTORA pieces that were affected by this violation and the action taken by Cephalon for the respective pieces.”	TEVA_MDL_A_01089145

Warning Letter

ACTAVIS			
Product	Date	Contents	BATES
Kadian	2/18/2010	<p>FDA sent a Warning Letter to Doug Boothe, Chief Executive Officer for Actavis US on February 18, 2010. The Warning Letter is addressed in greater detail in my report. The following includes some relevant portions.</p> <p>Statements:</p> <p>“Why is pain management Important? Pain management is a large part of your overall health care plan. Many Americans suffer from chronic or ongoing pain...Managing your pain the right way begins by talking to your healthcare provider. Discover the cause of your pain by taking note of what makes your pain start and what makes it worse.”</p> <p>“What Is chronic pain? Chronic pain is ongoing and can last longer than 6 months. Chronic pain can be mild or severe....”</p> <p>“How can I treat my chronic pain? To help manage your pain, your healthcare provider will determine what level of pain control you need. Depending on what kind of pain you have and how it affects your life, your healthcare provider will choose a drug that works just for you.”</p> <p>Misleading claims:</p> <p>“Allow for less breakthrough pain and more consistent pain relief for patients”</p> <p>“Better pain control...”</p> <p>“Improved pain control...”</p> <p>“Allow patients to live with less pain...”</p> <p>“Allow individualization and customization of a patient’s pain treatment”</p> <p>“Prescribe KADIAN – Less pain for you patients. More options for you.”</p> <p>“Less Pain. More Options.”</p>	ALLERGAN_MDL_01871597

		<p>FDA found the promotional materials were also misleading in that they imply that a drug product is indicated for use in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.</p> <p>Violations: The Warning Letter addressed, among other issues:</p> <ul style="list-style-type: none"> 4. Omission and Minimization of Risk Information 5. Broadening of Indication/Failure to State Full Indication 6. Unsubstantiated Superiority Claims 7. Unsubstantiated Effectiveness Claims <p>FDA Conclusion and Requested Actions:</p> <ul style="list-style-type: none"> 1. immediately cease the dissemination of violative promotional materials for Kadian; 2. to provide a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages to the audience(s) that received the violative promotional materials. 	
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Company Response to Warning Letter

ACTAVIS			
Product	Date	Contents	BATES
Kadian	3/4/2010	<p>Relevant Excerpts of Response</p> <p>“Actavis has already instructed its sales force to cease use and distribution of the two promotional materials identified in the Warning Letter. Any employees in possession of these materials have been instructed to return the materials... at which time they will be destroyed.”</p> <p>“Actavis has reviewed all Kadian promotional materials (as well as the Kadian website) to identify representations and claims similar to those that DDMAC identified as violative. Based on this review, Actavis has determined that each of the Kadian hard-copy promotional materials that are currently in use incorporate claims of concern to DDMAC. Thus, Actavis has made the decision to cease use and distribution of each of these hard-copy promotional materials, and Actavis has already instructed its sales force of this decision.”</p> <p>“As with the two pieces identified in the Warning Letter, Actavis has instructed employees in possession of these materials to return the materials to the Digital Direct warehouse for destruction. In addition, the field sales force has been instructed to retrieve any affected Kadian promotional materials remaining in the field by removing the materials from a physician’s office whenever possible and returning those materials to the warehouse for destruction.”</p> <p>“With respect to the Kadian website, Actavis has carefully reviewed the website’s content and format, and is in the process of revising the website to address the issues raised in the Warning Letter.”</p> <p>“In addition, Actavis commits that, going forward, any new Kadian promotional materials will incorporate changes addressing the issues raised in DDMAC’s Warning Letter</p>	ALLERGAN_MDL_01871610

		<p>and all applicable FDA regulations.”</p> <p>“As a further corrective measure, Actavis is revising its Standard Operating Procedure for reviewing and approving promotional labeling and advertising. The SOP will require that a committee comprising personnel from the Regulatory Affairs, Medical Affairs, Legal, and Marketing Departments review all promotional labeling and advertising before release of that material for dissemination. Previously, the SOP only required a more limited pre-clearance review. A committee review will provide a more rigorous and balanced review of materials.”</p> <p>“Finally, Actavis intends to conduct training of the Kadian sales force team to ensure that it understands the content of the corrective letters and can appropriately communicate that message to physicians during office visits.”</p>	
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FDA and Actavis continued to exchange correspondence concerning the Warning Letter and related response over several months. Correspondence appears to have been sent on March 5, 2010,¹ April 9, 2010,² April 19, 2010, April 23, 2010,³ May 3, 2010,⁴ May 20, 2010, May 26, 2010,⁵ June 10, 2010,⁶ July 6, 2010, July 12, 2010,⁷ and July 16, 2010.⁸

Actavis also held a training class on September 12, 2012 that addressed, among other issues, the Warning Letter and REMS for Kadian.⁹

¹ ALLERGAN_MDL_01871633

² ALLERGAN_MDL_01871496

³ ALLERGAN_MDL_01871640

⁴ ALLERGAN_MDL_01871522

⁵ ALLERGAN_MDL_01871539

⁶ ALLERGAN_MDL_01871543

⁷ ALLERGAN_MDL_01871572

⁸ ALLERGAN_MDL_01871577

⁹ ALLERGAN_MDL_00007770

SCHEDULE 7

Timeline of FDA Advisory Committee Meetings Concerning Oral Opioids, 1997-2018

Source: FDA Advisory Committee Webpage and FDA Archives
 Accessible at: <https://www.fda.gov/AdvisoryCommittees/default.htm>

Date	Meeting Subject and Vote Outcome	Voting Question and Outcomes (Yes-No-Abstain)
9/17/1997	Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) to discuss Cephalon's NDA for its Oral Transmucosal Fentanyl Citrate product, Actiq.	"Does the expected benefit to the intended clinical population outweigh the risk of accidental injury inherent in this product?" 16-0-0
5/28/1998	Meeting of the Drug Abuse Advisory Committee (DAAC) to discuss the abuse potential of tramadol.	The committee did not vote.
1/30/2002 – 1/31/2002	Meeting of ALSDAC to discuss the target population of various opioid populations, the need to assess sustained efficacy over the duration of a clinical trial for opioid efficacy, and Risk Management Programs (RMPs) for opioid drugs. The committee also discussed use of opioid analgesics in pediatric patients.	The committee did not vote.
9/9/2003 – 9/10/2003	Meeting of ALSDAC to discuss RMPs for opioid drugs, and the specific elements they should include: prescriber education, surveillance of misuse, abuse and diversion, assessment of source of diverted drugs, and assessment of RMP on opioid prescribing practices. The committee also discussed the RMP for Purdue Pharma's Palladone (hydromorphone ER).	The committee did not vote.
5/5/2008	Joint meeting of ALSDAC and DSaRM committees to discuss Purdue Pharma's NDA for reformulated Oxycontin (oxycodone ER) tablets that is intended to have abuse deterrent properties.	The committee did not vote.

Date	Meeting Subject and Vote Outcome	Voting Question and Outcomes (Yes-No-Abstain)
5/6/2008	Joint meeting of ALSDAC and DSaRM committees to discuss Cephalon's sNDA for Fentora (fentanyl buccal tablet) and its safety for the proposed indication of breakthrough pain in opioid tolerant non-cancer patients with chronic pain. The committee voted 3-17-0 against recommending approval of the indication.	"Considering your responses to the earlier questions, do you recommend approval of the expansion of the indication for Fentora to opioid-tolerant, non-cancer, chronic pain patients with breakthrough pain?" 3-17-0
11/13/2008	Meeting of ALSDAC to discuss Pain Therapeutics' NDA for Remoxy XRT (oxycodone ER) capsules that is intended to have abuse deterrent properties.	The committee did not vote.
11/14/2008	Meeting of ALSDAC to discuss Alpharma Pharmaceuticals' NDA for Emeda (morphine sulfate ER and naltrexone) tablets that is intended to have abuse deterrent properties.	The committee did not vote.
1/30/2009	Joint meeting of ALSDAC and DSaRM committees to discuss "the safety and efficacy of propoxyphene and propoxyphenecombination products for the treatment of mild to moderate acute pain."	"Based on the data presented, does the balance of risk and benefit support continued marketing of propoxyphene-containing products for the management of mild to moderate pain?" 12-14-0
9/23/2009	Joint meeting of ALSDAC and DSaRM committees to discuss Neuromed Pharmaceuticals' NDA for Exalgo (hydromorphone ER) tablets.	The committee did not vote.
9/24/2009	Joint meeting of ALSDAC and DSaRM committees to discuss Purdue Pharma's resubmitted NDA for reformulated Oxycontin (oxycodone ER) tablets that is intended to have abuse deterrent properties.	"Should this application for a reformulated OxyContin should be approved?" 14-4-1

Date	Meeting Subject and Vote Outcome	Voting Question and Outcomes (Yes-No-Abstain)
4/22/2010	Joint meeting of ALSDAC and DSaRM committees to discuss Acura Pharmaceuticals' NDA for Acurox (oxycodone and niacin) tablets that is intended to have abuse deterrent properties.	"Please vote on whether Acurox should be approved for the indication of the treatment of moderate to severe pain taking into consideration your conclusion regarding the deterrent effect of the niacin, as well as the potential deterrent effects of the other features specific to the Acurox formulation of oxycodone." 1-19-0
7/22/2010 – 7/23/2010	Joint meeting of ALSDAC and DSaRM committees to discuss the Agency's proposal for a class-wide REMS for ER/LA opioid analgesics.	"Please vote on whether you agree with the Agency's proposed REMS for extended release and long-acting opioid analgesics and discuss the rationale for your vote." 10-25-0
10/21/2010 – 10/22/2010	Joint meeting of ALSDAC and DSaRM committees to discuss the design of postmarketing studies to assess the effect of reformulated Oxycontin and Embeda, both formulated with properties intended to deter abuse, on outcomes related to misuse, abuse and their consequences.	The committee did not vote.
12/7/2012	Meeting of Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) to discuss Zogenix's NDA for Zohydro ER (hydrocodone bitartrate ER) capsules.	"Has the Applicant demonstrated that Zohydro ER is effective for the management of moderate to severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time?" 7-6-1 "Has the Applicant demonstrated that Zohydro ER is safe in the intended population?" 5-9-0
1/24/2013 – 1/25/2013	Meeting of DSaRM to discuss "the public health benefits and risks, including the potential for abuse, of drugs containing hydrocodone either combined with other analgesics or as an antitussive."	"Based on the background materials, presentations and the discussion above, do you recommend that hydrocodone combination products be rescheduled from schedule III to schedule II of the Controlled Substances Act (CSA)?" 19-0-0

Date	Meeting Subject and Vote Outcome	Voting Question and Outcomes (Yes-No-Abstain)
4/22/2014	Meeting of AADPAC to discuss QRxPharma's NDA for MoxDuo (morphine sulfate and oxycodone hydrochloride) capsules.	<p>"Given the available safety data, has the Applicant provided evidence that Moxduo is safer than morphine and oxycodone when these drugs are used individually and at comparable doses?"</p> <p>0-14-0</p> <p>:Should Moxduo be approved for the management of moderate to severe acute pain where the use of an opioid analgesic is appropriate?"</p> <p>0-14-0</p>
9/10/2015	Joint meeting of AADPAC and DSaRM committees to discuss Purdue Pharma's NDA for Aviridi (oxycodone IR) tablets that is intended to have abuse deterrent properties.	<p>"Should AVRIDI be approved for marketing in the US?"</p> <p>1-23-0</p>
9/11/2015	Joint meeting of AADPAC and DSaRM committees to discuss Collegium Pharmaceuticals' Xtampza ER (oxycodone ER) that is intended to have abuse deterrent properties.	<p>"Should XTAMPZA ER be approved for marketing in the US?"</p> <p>23-0-0</p>
5/3/2016 – 5/4/2016	Joint meeting of AADPAC and DSaRM to discuss results from assessments of the extended-release and long-acting (ER/LA) Opioid Analgesics REMS.	<p>"Considering all available information, which one of the following options do you recommend FDA pursue regarding the ER/LA Opioid Analgesics REMS?"</p> <p>A. Continue without modifications</p> <p>B. Eliminate the REMS</p> <p>C. Modify the REMS"</p> <p>0-0-30</p>
5/5/2016	Joint meeting of AADPAC and DSaRM to discuss KemPharm's NDA for a novel formulation of benzhydrocodone and acetaminophen IR tablets formulated with properties intended to deter abuse.	<p>"Should KP201/APAP be approved for the proposed indication?"</p> <p>16-4-0</p> <p>"If approved, should KP201/APAP be labeled as an abuse-deterrent product?"</p> <p>2-18-0</p>

Date	Meeting Subject and Vote Outcome	Voting Question and Outcomes (Yes-No-Abstain)
6/7/2016	Joint meeting of AADPAC and DSaRM to discuss Teva's NDA for a novel formulation of hydrocodone bitartrate ER tablets formulated with properties intended to deter abuse. The committee voted 2-18-0 against abuse deterrent labeling. The committee also voted 14-3-0 in favor of recommending approval of the NDA.	<p>“Should Vantrela ER be approved for the proposed indication, management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate?” 14-3-0</p> <p>“If approved, should Vantrela ER be labeled as an abuse-deterrent product by the oral route of abuse?” 14-3-0</p> <p>“If approved, should Vantrela ER be labeled as an abuse-deterrent product by the nasal route of abuse?” 14-3-0</p> <p>“If approved, should Vantrela ER be labeled as an abuse-deterrent product by the intravenous route of abuse?” 16-1-0</p>
6/8/2016	Joint meeting of AADPAC and DSaRM to discuss Pfizer's NDA for a novel formulation of oxycodone and naltrexone ER capsules formulated with properties intended to deter abuse.	<p>“Should Troxyca ER be approved for the proposed indication, management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate?” 9-6-0</p> <p>“If approved, should Troxyca ER be labeled as an abuse-deterrent product by the oral route of abuse?” 6-9-0</p> <p>“If approved, should Troxyca ER be labeled as an abuse-deterrent product by the nasal route of abuse?” 11-4-0</p> <p>“If approved, should Troxyca ER be labeled as an abuse-deterrent product by the intravenous route of abuse?” 9-6-0</p>

Date	Meeting Subject and Vote Outcome	Voting Question and Outcomes (Yes-No-Abstain)
8/14/2016	Joint meeting of AADPAC and DSaRM to discuss Egalet US' NDA for a novel formulation of morphine sulfate ER tablets formulated with properties intended to deter abuse.	<p>“If approved, should Arymo ER be labeled as an abuse-deterrent product by the oral route of abuse?” 16-3-0</p> <p>“If approved, should Arymo ER be labeled as an abuse-deterrent product by the nasal route of abuse?” 18-1-0</p> <p>“If approved, should Arymo ER be labeled as an abuse-deterrent product by the intravenous route of abuse?” 18-1-0</p> <p>“Should Arymo ER be approved for the proposed indication, management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate?” 18-1-0</p>
9/15/2016- 9/16/2016	Joint meeting of AADPAC, DSaRM and the Pediatric Advisory Committee (PAC) to discuss “the appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients.”	The committee did not vote.
10/5/2016	Joint meeting of AADPAC and DSaRM discusses naloxone products intended for use in the community, specifically the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages.	<p>“Is the pharmacokinetic standard based on 0.4 mg of naloxone given by an approved route (IV, IM, SQ) appropriate for approval of naloxone products for use in the community or are higher doses and/or exposures required?” 15-13-0</p> <p>“Should there be different minimum standards used to support the approval of products intended for use in adults and in children?” 7-21-0</p>

Date	Meeting Subject and Vote Outcome	Voting Question and Outcomes (Yes-No-Abstain)
3/13/2017- 3/14/2017	Joint meeting of AADPAC and DSaRM to discuss safety issues of Endo Pharmaceuticals' Opana ER oxymorphone extended release tablets. The committee voted 8-18-01 that benefits of reformulated Opana ER no longer outweigh the risks, but in discussion those voting "no" were split on whether the drug should be removed from the market.	"Do the benefits of reformulated Opana ER continue to outweigh its risks" 8-18-1
4/5/2017	Joint meeting of AADPAC and DSaRM to discuss Inspirion Delivery Sciences' NDA for a novel formulation of oxycodone IR tablets formulated with properties intended to deter abuse.	"If approved, should RoxyBond be labeled as an abuse-deterrent product by the nasal route of abuse?" 19-1-0 "If approved, should RoxyBond be labeled as an abuse-deterrent product by the intravenous route of abuse?" 16-4-0 "Should RoxyBond be approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate?" 19-0-1
7/26/2017	Joint meeting of AADPAC and DSaRM to discuss Intellipharma's NDA for a novel formulation of oxycodone ER tablets formulated with properties intended to deter abuse.	"Has the Applicant demonstrated that oxycodone extended-release tablets have properties that can be expected to deter abuse by the IV route of administration?" 4-19-0 "Are there sufficient data for this product to support inclusion of language regarding abuse-deterrent properties in the product label for the IV route of administration?" 0-23-0 "Should this drug product, Oxycodone HCl ER tablets, be approved?" 1-22-0

Date	Meeting Subject and Vote Outcome	Voting Question and Outcomes (Yes-No-Abstain)
9/11/2017	PAC discusses the use of prescription opioid products containing hydrocodone or codeine for the treatment of cough in pediatric patients. The discussion included current practice for the treatment of cough in children and benefit-risk considerations regarding the use of prescription opioid products in pediatric patients.	<p>“Is the benefit/risk favorable for use of prescription codeine cough suppressants for treatment of cough associated with allergy or the common cold in pediatric patients 12 to < 18 years of age?” 0-24-0</p> <p>“Is the benefit/risk favorable for use of hydrocodone cough suppressants for treatment of cough associated with allergy or the common cold in pediatric patients: 6<12 years? Yes or No” 1-23-0</p> <p>“12<18 years? Yes or No” 1-23-0</p> <p>“Is the benefit/risk favorable for use of prescription opioid cough suppressants for treatment of cough in pediatric patients?” 2-31-0</p>
9/14/2017	Joint meeting of AADPAC and DSaRM to discuss Purdue Pharma’s sNDA for Butrans (buprenorphine) transdermal system for pediatric use.	The committee did not vote.
2/14/2018 2/15/2018	Joint meeting of AADPAC and DSaRM to discuss Charleston Laboratories’ NDA for a novel combination oral tablet containing hydrocodone, acetaminophen, and promethazine for the short term treatment of acute pain.	<p>“Should Hydexor be approved?” 2-19-0</p>

Date	Meeting Subject and Vote Outcome	Voting Question and Outcomes (Yes-No-Abstain)
3/27/2018	Meeting of the Psychopharmacologic Drugs Advisory Committee to discuss US WorldMeds' NDA for lofexidine hydrochloride for mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment. The committee voted 12-0-0 in favor of the proposition, "." The committee also voted 11-1-0 in favor of recommending approval of the NDA.	"Do the data provide substantial evidence of effectiveness of lofexidine for the mitigation of symptoms associated with opioid withdrawal?" 12-0-0 "Do you recommend approval of this application?" 1-11-0
5/22/2018	Joint meeting of AADPAC and DSaRM to discuss INSYS Development Company's NDA for a buprenorphine sublingual spray.	"Overall, do the benefits of Buvaya outweigh the risks for the indication, 'the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate,' supporting approval of Buvaya?" 1-18-0
7/26/2018	Joint meeting of AADPAC and DSaRM to discuss Pain Therapeutics' NDA for a novel formulation of oxycodone ER capsules that is intended to have abuse deterrent properties.	"Based on the data presented and the discussions about the data, do the efficacy, safety and risk-benefit profile of Remoxy ER support the approval of this application?" 3-14-0
8/3/2018	Joint meeting of AADPAC and DSaRM to discuss the results from the TIRF REMS assessments.	The committee did not vote.
10/12/2018	Meeting of AADPAC to discuss AcelRx Pharmaceutical's NDA for sufentanil sublingual tablets.	"Overall, do the benefits of sufentanil sublingual tablets 30 mcg with the REMS proposed by FDA outweigh the risks for the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting, supporting approval of sufentanil sublingual tablets 30 mcg?" 10-3-0

Date	Meeting Subject and Vote Outcome	Voting Question and Outcomes (Yes-No-Abstain)
11/14/2018	Joint meeting of AADPAC and DSaRM to discuss SpecGx's NDA for a novel formulation of IR Oxycodone intended to resist common methods of tampering.	<p>"If approved, should oxycodone hydrochloride immediate-release tablets (MNK-812) be labeled as an abuse-deterrent product by the nasal route of abuse?" 12-5-0</p> <p>"If approved, should oxycodone hydrochloride immediate-release tablets (MNK-812) be labeled as an abuse-deterrent product by the intravenous route of abuse?" 7-10-0</p> <p>"Should oxycodone hydrochloride immediate-release tablets (MNK-812) be approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate?" 10-7-0</p>
11/15/2018	Meeting of AADPAC to discuss the assessment of opioid analgesic sparing outcomes in clinical trials of acute pain and the trial design and endpoints of these studies and how to determine the clinical relevance of the results.	<p>"Is any reduction in opioid use sufficient to warrant labeling as opioid sparing?" 1-11-1</p> <p>"Is it sufficient to claim opioid-level analgesia for a novel analgesic based on the clinical trial population and without an opioid active comparator?" 1-12-0</p>
12/17/2018- 12/18/2018	Joint meeting of AADPAC and DSaRM to discuss strategies to increase the availability of naloxone products intended for use in the community.	<p>"Would labeling language that recommends co-prescription of naloxone for all or some patients prescribed opioids, or more targeted prescribing for patients otherwise at high risk for death from opioid overdose be an effective method for expanding access to naloxone and improving public health?" 12-11-0</p>

SCHEDULE 8

ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Sales Period		Promotion	Wholesale	Retail	
Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
ABSTRAL	JAN2011	MAY2018	33,389	70,280,073	46,413,354	805,325
ACTIQ	JAN1999	MAY2018	138,689	2,591,552,362	12,015,444,194	114,696,272
ALOR	AUG1995	MAY2003	6,845	398,067	5,936,560	1,187,312
ANEXSIA	JAN1993	NOV2013	202,968	37,593,299	514,862,731	72,252,393
ANOLOR DH	JAN1993	FEB2003	.	140,485	10,938,155	2,187,631
AVINZA	JAN2002	MAY2018	482,085	1,511,822,464	14,333,238,045	203,489,466
BANCAP-HC	JAN1993	JAN2010	.	3,990,021	23,620,685	4,724,137
BUTRANS	OCT2010	MAY2018	936,856	1,351,300,636	2,541,126,263	16,397,778
CETA	AUG1994	NOV2005	603	33,707	1,353,735	270,747
CO-GESIC	JAN1993	FEB2014	13,689	4,035,095	63,297,380	12,659,476
CODEINE	JAN1993	SEP2013	.	275,945	8,126,838	1,405,695
CODEINE PHOSPHATE	JAN1993	DEC2013	.	6,788,371	50,371,563	11,436,504
CODEINE SULFATE	JAN1993	MAY2018	193	104,351,681	1,038,731,735	188,635,729
COMBUNOX	DEC2004	SEP2015	178,304	22,048,106	96,597,135	12,879,618
DAMASON	JAN1993	APR2010	1,820	4,490,106	48,213,125	9,642,625
DEMEROL	JAN1993	MAY2018	466	156,782,838	936,474,896	170,234,783
DEMEROL/APAP	JAN1993	JUN2002	.	506	196,600	39,320
DILAUDID	JAN1993	MAY2018	33,764	374,834,379	6,202,032,144	425,536,718
DOLAGESIC	JAN1996	NOV2008	.	15,796	2,928,330	585,666
DOLOREX FORTE	FEB2001	JUN2011	.	65	9,370	1,874
DURADYNE DHC	JAN1993	DEC1997	.	316	13,170	2,634
DURAGESIC	JAN1993	MAY2018	754,513	9,362,870,201	128,864,615,292	308,569,180
EMBEDA	JAN2009	MAY2018	223,728	280,811,796	1,041,962,850	26,979,678
ENDOCET	JUN1994	MAY2018	971	1,650,265,256	54,325,909,133	4,640,338,658
ENDOCODONE	JAN1999	SEP2011	.	194,865	23,996,168	3,199,489
ENDODAN	JUL1994	MAR2018	.	25,240,453	824,712,901	112,696,272

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Sales Period		Promotion	Wholesale	Retail	
Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
ETH-OXYDOSE	JAN2001	FEB2016	.	37,171,282	1,582,677,030	52,755,901
EXALGO	JAN2010	MAY2018	170,646	723,155,200	1,852,300,544	32,091,412
FENTANYL	JAN2005	MAY2018	8,845	9,489,771,439	300,450,531,038	769,879,769
FENTANYL CIT	JAN2006	MAY2018	.	1,698,177,571	9,185,746,596	82,350,980
FENTORA	JAN2006	MAY2018	230,009	1,913,756,525	2,528,626,490	39,827,626
HY-5	FEB1993	AUG1995	.	.	970	194
HY-PHEN	JAN1993	MAR2011	.	885,455	22,272,075	4,454,415
HYCET	JAN2004	MAY2018	11,895	15,125,032	32,074,668	64,149,336
HYCOMED	JAN1994	JUN2001	200	61,759	1,448,595	284,785
HYDROCET	JAN1993	FEB2015	11,304	3,216,320	75,448,855	15,089,771
HYDROCODONE/APAP	JAN1993	MAY2018	7,300	11,187,459,460	795,445,820,018	111,795,466,858
HYDROCODONE/IBUPROFEN	JAN2003	MAY2018	156	572,899,635	9,189,056,395	1,222,701,575
HYDROGESIC	JAN1993	JAN2014	82	257,039	7,079,148	960,859
HYDROMORPHONE	JAN1993	MAY2018	160	660,016,167	52,153,185,612	3,241,804,264
HYDROMORPHONE ER	MAY2014	MAY2018	.	362,509,192	1,173,477,792	19,334,868
HYDROSTAT	OCT1993	FEB2002	.	132,138	4,992,752	400,162
IBUDONE	JAN2008	MAY2018	7,962	7,116,006	43,970,135	5,059,108
KADIAN	JUL1996	MAY2018	297,338	2,222,255,897	17,511,232,930	344,338,423
LAZANDA	JAN2011	MAY2018	28,032	97,663,789	5,537,616	137,863
LIQUICET	JAN2007	MAR2012	.	46,403	103,160	10,316
LORCET	JAN1993	MAY2018	360,380	594,912,218	7,531,132,493	870,690,552
LORPAC	NOV1993	NOV1993	.	.	760	152
LORTAB	JAN1993	MAY2018	629,014	920,496,016	9,458,735,270	1,850,332,039
MAGNACET	JAN2007	MAR2017	18,178	16,804,419	69,793,710	5,284,062
MARGESIC H	JAN1993	DEC2011	1,193	651,816	11,567,215	2,313,443
MAXIDONE	JAN2000	JUL2014	48,981	16,687,126	113,454,640	11,345,464

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Sales Period		Promotion	Wholesale	Retail	
Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
MEPERGAN	JAN1993	AUG2015	169	35,626,496	251,735,760	50,347,152
MEPERIDINE	JAN1993	MAY2018	283	125,008,136	2,004,133,150	369,046,667
MEPERIDINE/PROMETH	APR1993	MAY2018	.	15,427,920	302,855,440	60,571,088
MEPERITAB	JAN1996	DEC2010	.	9,352,935	147,823,135	25,588,372
MEPROZINE	APR1993	MAR2015	.	45,315,931	680,654,350	136,130,870
MORPHINE SULFATE	JAN1993	MAY2018	5,980	4,674,616,152	269,971,679,076	8,352,447,019
MORPHINE SULFATE IR	JAN2001	DEC2002	9	3,133,974	482,284,965	21,806,017
MS-CONTIN	JAN1993	MAY2018	202,563	1,629,252,698	29,634,677,895	636,328,836
MS/L	FEB1994	FEB2008	.	287,859	580,952	290,476
MS/S	MAR1994	NOV2003	.	85,053	670,715	43,370
MSIR	JAN1993	JAN2018	21,665	39,843,574	2,804,518,156	130,696,318
NORCO	MAR1997	MAY2018	167,010	483,446,955	4,255,589,613	447,585,319
NUCYNTA	JAN2009	MAY2018	803,894	1,564,310,251	11,839,520,450	412,461,321
NUCYNTA ER	JAN2011	MAY2018	211,230	981,605,812	5,712,869,640	110,541,964
NUMORPHAN	JAN1993	MAR2007	1,042	1,803,067	4,449,420	296,628
OMS	JAN1993	JUN2002	.	593,090	22,853,960	1,142,698
ONCET	JAN1993	FEB1999	706	66,205	966,190	193,238
ONSOLIS	JAN2009	APR2018	7,423	393,120	51,336	907
OPANA	JAN2006	MAY2018	154,176	250,318,418	1,525,032,630	61,559,984
OPANA ER	JAN2006	MAY2018	318,136	3,576,884,988	32,879,291,498	457,491,761
OPIUM	JAN1993	MAY2018	.	208,291,410	917,339,580	91,733,958
ORALET	MAR1995	DEC2006	5,227	1,137,251	72,813	3,047
ORAMORPH SR	JAN1993	JUL2016	75,090	279,428,522	6,427,385,820	138,183,145
OXYCODONE	APR1996	MAY2018	1,082	4,433,427,422	392,005,994,900	17,799,236,084
OXYCODONE ER	JAN2004	MAY2018	16	4,594,753,698	84,873,397,590	1,573,400,852
OXYCODONE/APAP	JAN1993	MAY2018	515	5,756,773,769	271,736,614,845	25,985,944,672

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Sales Period		Promotion	Wholesale	Retail	
Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
OXYCODONE/ASA	JAN1993	MAY2018	.	50,090,547	724,273,649	98,665,574
OXYCODONE/IBUPROF	JAN2007	MAY2018	.	4,386,711	30,057,720	4,007,696
OXYCONTIN	DEC1995	MAY2018	1,938,164	37,764,087,426	376,515,274,808	7,184,085,949
OXYFAST	OCT1998	JAN2015	21,946	29,703,509	609,493,320	20,316,444
OXYIR	JAN1996	JUL2016	51,246	47,613,176	1,168,757,550	155,834,340
OXYMORPHONE	JAN2010	MAY2018	.	398,021,001	3,694,574,775	141,661,942
OXYMORPHONE ER	JAN2011	MAY2018	1,565	779,352,289	8,374,276,328	128,920,591
PALLADONE	OCT2004	JUL2009	22,143	20,156,318	74,778,736	953,345
PANLOR	JAN1993	MAR2018	37,697	200,265	5,858,670	1,171,734
PERCOCET	JAN1993	MAY2018	163,297	2,838,481,024	14,815,728,773	1,455,735,510
PERCODAN	JAN1993	JAN2017	9,297	114,851,446	1,007,368,745	137,686,930
PERCODAN-DEMI	JAN1993	DEC2005	.	986,545	3,067,395	838,086
PERCOLONE	NOV1997	AUG2007	8,834	1,468,205	4,522,335	602,978
PERLOXX	JAN2006	JAN2011	1,745	582,600	3,360,315	277,709
POLYGESIC	JAN1993	MAY2013	198	206,219	1,617,375	323,475
PRIMLEV	JAN2008	MAY2018	14,273	21,641,372	51,702,285	3,905,268
PROCET	JAN2001	JUL2011	170	998,441	2,365,053	332,308
R.M.S.	JAN1993	MAR2013	.	5,704,804	49,402,155	3,459,628
REPREXAIN	JAN2004	APR2018	64,690	27,969,661	147,915,463	17,584,815
ROXANOL	JAN1993	MAY2018	13,261	96,772,601	4,748,817,805	237,525,933
ROXICET	JAN1993	MAY2018	2,155	289,657,921	23,620,323,423	3,196,649,350
ROXICODONE	JAN1993	MAY2018	24,390	396,303,074	8,093,892,026	571,633,888
ROXILOX	JAN1993	DEC1997	12	.	781,409,633	104,187,951
ROXIPRIN	JAN1993	APR2011	115	7,352,614	503,974,420	68,849,121
STAGESIC	JAN1993	FEB2016	8,009	2,603,406	67,230,120	12,865,034
SUBSYS	JAN2012	MAY2018	94,710	1,458,491,889	2,166,317,136	16,914,066

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Sales Period		Promotion	Wholesale	Retail	
Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
TYLOX	JAN1993	FEB2014	2,318	156,113,829	1,273,352,393	169,780,319
ULTRAGESIC	JAN1993	JAN1997	186	11,010	1,819,890	363,978
VANACET	JAN1993	NOV2009	1,494	204,505	5,507,295	1,101,459
VICODIN	JAN1993	MAY2018	150,925	487,889,447	4,532,783,150	906,556,630
VICODIN ES	JAN1993	MAY2018	108,112	641,982,430	7,691,299,598	1,025,506,613
VICODIN HP	OCT1996	MAY2018	28,058	122,018,236	1,271,734,270	127,173,427
VICOPROFEN	SEP1997	APR2018	491,701	524,154,478	3,563,056,050	475,074,140
XARTEMIS XR	MAR2014	MAY2018	60,199	13,471,890	48,875,321	4,344,473
XODOL	JAN2004	APR2018	73,588	51,903,206	313,404,350	33,347,048
XOLOX	JAN2009	JAN2014	9,251	2,344,872	16,341,330	1,089,422
XYLON	JAN2015	NOV2017	.	.	1,708,120	170,812
ZAMICET	JAN2008	MAY2018	13,071	9,830,487	21,532,529	32,138,103
ZOXYDRO ER	FEB2014	MAY2018	100,577	147,782,177	416,196,180	17,125,590
ZOLVIT	JAN2010	MAR2016	3,584	1,051,186	2,641,468	3,942,489
ZYDNE	JAN1993	JAN2017	125,605	64,713,176	872,873,090	103,604,434
			10,463,360	123,393,683,492	3,017,253,917,778	200,101,299,542

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
ABSTRAL	Non	Non-Defendant	Non-Defendant	JAN2011	MAY2018	33,389	70,280,073	46,413,354	805,325
ABSTRAL						33,389	70,280,073	46,413,354	805,325
ACTIQ	Def	Teva	ANESTA CORPORATION	APR2000	FEB2001	7,793	.	.	.
			CEPHALON INC	JAN1999	NOV2011	103,920	1,266,719,433	10,586,953,572	101,912,783
			TEVA	JAN2006	MAY2018	24,054	1,324,832,929	1,428,490,622	12,783,489
	Non	Non-Defendant	Non-Defendant	FEB1999	MAR2000	2,922	.	.	.
ACTIQ						138,689	2,591,552,362	12,015,444,194	114,696,272
ALOR	Non	Non-Defendant	Non-Defendant	AUG1995	MAY2003	6,845	398,067	5,936,560	1,187,312
ALOR						6,845	398,067	5,936,560	1,187,312
ANEXSIA	Def	Actavis	ACTAVIS	JAN2008	SEP2011	.	52	78,423	14,126
			ANDRX	DEC2001	SEP2003	55,246	.	.	.
			WATSON LABS	JAN2001	DEC2007	.	8,693,102	63,687,260	9,564,942
		Mallinckrodt	MALLINCKRODT	JAN1993	JAN2013	1,732	28,900,145	451,095,329	62,672,981
		Teva	TEVA	JUN2012	NOV2013	.	.	1,720	344
		Non-Defendant	Non-Defendant	JAN1993	NOV1995	145,990	.	.	.
ANEXSIA						202,968	37,593,299	514,862,731	72,252,393
ANOLOR DH	Non	Non-Defendant	Non-Defendant	JAN1993	FEB2003	.	140,485	10,938,155	2,187,631
ANOLOR DH						.	140,485	10,938,155	2,187,631
AVINZA	Non	Non-Defendant	Non-Defendant	JAN2002	MAY2018	482,085	1,511,822,464	14,333,238,045	203,489,466

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
AVINZA						482,085	1,511,822,464	14,333,238,045	203,489,466
BANCAP-HC	Def	Actavis	ACTAVIS	JUL2009	JAN2010	.	.	1,055	211
			FOREST PHARM	JAN1993	DEC2007	.	611,158	23,619,630	4,723,926
		Teva	TEVA	JAN1993	DEC1998	.	3,378,863	.	.
BANCAP-HC						.	3,990,021	23,620,685	4,724,137
BUTRANS	Def	Purdue	PURDUE	OCT2010	MAY2018	936,856	1,351,300,636	2,541,126,263	16,397,778
BUTRANS						936,856	1,351,300,636	2,541,126,263	16,397,778
CETA	Non	Non-Defendant	Non-Defendant	AUG1994	NOV2005	603	33,707	1,353,735	270,747
CETA						603	33,707	1,353,735	270,747
CO-GESIC	Non	Non-Defendant	Non-Defendant	JAN1993	FEB2014	13,689	4,035,095	63,297,380	12,659,476
CO-GESIC						13,689	4,035,095	63,297,380	12,659,476
CODEINE	Def	Teva	TEVA	JUN1993	JUN1993	.	9,409	.	.
	Non	Non-Defendant	Non-Defendant	JAN1993	SEP2013	.	266,536	8,126,838	1,405,695
CODEINE						.	275,945	8,126,838	1,405,695
CODEINE PHOSPHATE	Non	Non-Defendant	Non-Defendant	JAN1993	DEC2013	.	6,788,371	50,371,563	11,436,504
CODEINE PHOSPHATE						.	6,788,371	50,371,563	11,436,504

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
CODEINE SULFATE	Def	Endo Labs	PAR PHARM	MAY2012	JAN2017	.	.	4,815	950
			QUALITEST PRODUCTS	JAN2009	NOV2011	.	121,137	1,453,995	245,907
	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	193	104,230,544	1,037,272,925	188,388,872
CODEINE SULFATE						193	104,351,681	1,038,731,735	188,635,729
COMBUNOX	Def	Actavis	ACTAVIS	JAN2009	DEC2010	.	480,290	2,634,818	351,309
			ALLERGAN	JAN2011	SEP2015	648	690	17,963	2,395
			FOREST PHARM	DEC2004	OCT2012	177,656	21,567,126	93,944,355	12,525,914
COMBUNOX						178,304	22,048,106	96,597,135	12,879,618
DAMASON	Non	Non-Defendant	Non-Defendant	JAN1993	APR2010	1,820	4,490,106	48,213,125	9,642,625
DAMASON						1,820	4,490,106	48,213,125	9,642,625
DEMEROL	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	466	156,782,838	936,474,896	170,234,783
DEMEROL						466	156,782,838	936,474,896	170,234,783
DEMEROL/APAP	Non	Non-Defendant	Non-Defendant	JAN1993	JUN2002	.	506	196,600	39,320
DEMEROL/APAP						.	506	196,600	39,320

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
DILAUDID	Def	Purdue	PURDUE	MAY1993	MAY2018	362	168,163,202	2,480,817,992	177,525,376
			RHODES PHARM	JAN1993	MAY2018	1,428	137,436,945	436,751,916	22,838,408
	Non	Non-Defendant	Non-Defendant	JAN1993	FEB2008	31,974	69,234,232	3,284,462,236	225,172,934
DILAUDID						33,764	374,834,379	6,202,032,144	425,536,718
DOLAGESIC	Non	Non-Defendant	Non-Defendant	JAN1996	NOV2008	.	15,796	2,928,330	585,666
DOLAGESIC						.	15,796	2,928,330	585,666
DOLOREX FORTE	Non	Non-Defendant	Non-Defendant	FEB2001	JUN2011	.	65	9,370	1,874
DOLOREX FORTE						.	65	9,370	1,874
DURADYNE DHC	Def	Actavis	FOREST PHARM	FEB1993	DEC1997	.	.	13,170	2,634
		Teva	TEVA	JAN1993	MAR1994	.	316	.	.
DURADYNE DHC						.	316	13,170	2,634
DURAGESIC	Def	Janssen	ALZA	AUG1994	JUN2002	2,470	.	.	.
			JANSSEN PHARM	JAN1993	MAY2018	713,327	9,362,870,201	128,864,615,292	308,569,180
			JOHNSON & JOHNSON	JAN2013	FEB2018	3,698	.	.	.
			MCNEIL	JAN2005	AUG2007	5,875	.	.	.
			ORTHO PHARM	SEP1995	OCT2007	23,422	.	.	.
			PRICARA	JAN2006	JUL2010	5,721	.	.	.
DURAGESIC						754,513	9,362,870,201	128,864,615,292	308,569,180
EMBEDA	Non	Non-Defendant	Non-Defendant	JAN2009	MAY2018	223,728	280,811,796	1,041,962,850	26,979,678

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
EMBEDA						223,728	280,811,796	1,041,962,850	26,979,678
ENDOCET	Def	Dupont	ENDO LABS	JUN1994	JUL1997	.	11,644,969	975,194,408	130,025,921
		Endo Labs	ENDO LABS	AUG1997	MAY2018	971	1,638,620,287	53,350,714,725	4,510,312,737
ENDOCET						971	1,650,265,256	54,325,909,133	4,640,338,658
ENDOCODONE	Def	Endo Labs	ENDO LABS	JAN1999	SEP2011	.	194,865	23,996,168	3,199,489
ENDOCODONE						.	194,865	23,996,168	3,199,489
ENDODAN	Def	Dupont	ENDO LABS	JUL1994	JUL1997	.	1,234,991	71,243,146	9,689,410
		Endo Labs	ENDO LABS	AUG1997	MAR2018	.	24,005,462	753,469,755	103,006,862
ENDODAN						.	25,240,453	824,712,901	112,696,272
ETH-OXYDOSE	Non	Non-Defendant	Non-Defendant	JAN2001	FEB2016	.	37,171,282	1,582,677,030	52,755,901
ETH-OXYDOSE						.	37,171,282	1,582,677,030	52,755,901
EXALGO	Def	Mallinckrodt	MALLINCKRODT	JAN2010	MAY2018	170,646	723,155,200	1,852,300,544	32,091,412
EXALGO						170,646	723,155,200	1,852,300,544	32,091,412
FENTANYL	Def	Actavis	ACTAVIS	JAN2008	DEC2011	.	726,633,462	21,540,905,100	51,020,755
			WATSON LABS	JAN2007	DEC2007	.	25,377,965	669,635,460	1,552,013

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
FENTANYL	Def	Endo Labs	DAVA PHARM	MAR2005	AUG2008	.	.	63,180	193
			PAR PHARM	JAN2007	DEC2011	.	179,953,654	5,301,198,180	12,368,406
		Mallinckrodt	MALLINCKRODT	JAN2011	MAY2018	170	723,472,390	28,776,567,787	71,032,836
		Teva	TEVA	JAN2008	MAY2018	242	529,669,088	33,598,421,820	81,999,815
	Non	Non-Defendant	Non-Defendant	JAN2005	MAY2018	8,433	7,304,664,880	210,563,739,511	551,905,751
FENTANYL						8,845	9,489,771,439	300,450,531,038	769,879,769
FENTANYL CIT	Def	Actavis	ACTAVIS	JAN2008	DEC2008	.	136,958,508	652,622,542	5,939,218
			WATSON LABS	JAN2006	DEC2007	.	216,176,727	854,520,628	7,927,174
		Endo Labs	PAR PHARM	JAN2011	MAY2018	.	95,166,994	673,742,732	5,999,216
		Mallinckrodt	MALLINCKRODT	JAN2010	MAY2018	.	258,602,303	1,501,307,106	12,752,357
		Teva	TEVA	JAN2006	MAY2018	.	991,273,039	5,503,421,300	49,731,436
	Non	Non-Defendant	Non-Defendant	JUN2010	MAR2015	.	.	132,288	1,579
FENTANYL CIT						.	1,698,177,571	9,185,746,596	82,350,980
FENTORA	Def	Teva	CEPHALON INC	OCT2006	DEC2011	105,707	.	46,246,473	933,398
			TEVA	JAN2006	MAY2018	124,302	1,913,756,525	2,482,380,017	38,894,228
FENTORA						230,009	1,913,756,525	2,528,626,490	39,827,626
HY-5	Def	Actavis	FOREST PHARM	FEB1993	AUG1995	.	.	970	194
HY-5						.	.	970	194
HY-PHEN	Non	Non-Defendant	Non-Defendant	JAN1993	MAR2011	.	885,455	22,272,075	4,454,415
HY-PHEN						.	885,455	22,272,075	4,454,415

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
HYCET	Non	Non-Defendant	Non-Defendant	JAN2004	MAY2018	11,895	15,125,032	32,074,668	64,149,336
HYCET						11,895	15,125,032	32,074,668	64,149,336
HYCOMED	Non	Non-Defendant	Non-Defendant	JAN1994	JUN2001	200	61,759	1,448,595	284,785
HYCOMED						200	61,759	1,448,595	284,785
HYDROCET	Non	Non-Defendant	Non-Defendant	JAN1993	FEB2015	11,304	3,216,320	75,448,855	15,089,771
HYDROCET						11,304	3,216,320	75,448,855	15,089,771
HYDROCODONE/APAP	Def	Actavis	ACTAVIS	JAN2008	DEC2011	.	1,094,222,377	97,933,365,828	12,569,926,878
			ROYCE LABS	MAR1996	SEP2007	.	1,716,548	201,633,420	29,722,584
			RUGBY LABS	JAN1993	DEC1993	.	.	241,093,140	42,670,981
			SCHEIN PHARM	JAN1993	DEC1996	.	.	331,060,138	59,766,894
			WARNER-CHILCOTT	JAN1993	DEC2008	.	1,668,276	2,198,325,548	346,524,029
			WATSON LABS	JAN1993	DEC2007	36	1,211,764,949	117,827,099,253	16,363,285,321
		Dupont	ENDO LABS	FEB1995	JUL1997	.	7,708,650	396,580,690	56,450,301
		Endo Labs	ENDO LABS	AUG1997	DEC2011	.	3,141,064	378,708,598	56,749,051
			PAR PHARM	JAN1993	MAY2018	.	2,039,282,198	79,399,814,123	10,668,318,591
			QUALITEST PRODUCTS	JAN1993	DEC2011	.	777,736,276	73,395,393,860	10,675,145,434
			VINTAGE PHARM	OCT1993	NOV2012	.	3,424,268	474,312,115	59,240,455
		Mallinckrodt	MALLINCKRODT	JAN1995	MAY2018	115	3,222,031,117	273,429,589,382	39,610,441,036
		Purdue	RHODES PHARM	MAY2016	MAY2018	.	8,927,847	582,668,383	73,565,982

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
HYDROCODONE/APAP	Def	Teva	BARR LABS	JAN1993	DEC2003	.	645,891	137,011,355	25,927,642
			IVAX	JAN1996	DEC2000	.	889,858	885,375,913	150,468,023
			TEVA	JAN1993	MAY2018	.	1,643,030,760	92,879,713,393	11,573,714,596
			ZENITH GOLDLINE	JAN1993	DEC1995	.	.	1,185,518,178	216,135,738
	Dist	AmerisourceBergen	AMERICAN HLTH PKG	JAN2002	MAY2018	.	33,326,592	8,037,783	1,294,557
		Cardinal	MAJOR PHARM	JAN1993	MAY2018	.	24,322,060	1,190,407,440	195,140,102
			PARMED PHARM	JAN1993	JAN2009	.	401,763	59,581,670	11,916,334
		McKesson	MCKESSON	JAN1999	MAY2018	.	24,532,033	42,860,838	7,698,442
	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	7,149	1,088,686,933	52,267,668,976	9,001,363,887
HYDROCODONE/APAP						7,300	11,187,459,460	795,445,820,018	111,795,466,858
HYDROCODONE/IBUPROFEN	Def	Actavis	ACTAVIS	JAN2008	DEC2011	.	33,102,016	1,155,080,160	154,010,688
			WATSON LABS	JAN2004	DEC2007	120	35,930,725	246,295,695	32,839,426
		Endo Labs	PAR PHARM	JAN2012	MAY2018	.	15,830,351	511,487,430	67,940,313
			QUALITEST PRODUCTS	JAN2006	DEC2011	.	11,540,416	283,733,198	37,831,093
		Teva	TEVA	JAN2003	MAY2018	36	258,058,296	4,745,683,020	632,757,736
	Dist	AmerisourceBergen	AMERICAN HLTH PKG	JAN2007	MAY2018	.	781,116	874,103	116,547
		McKesson	MCKESSON	JAN2012	MAR2018	.	50,078	18,540	2,472
	Non	Non-Defendant	Non-Defendant	JUN2003	MAY2018	.	217,606,637	2,245,884,250	297,203,300
HYDROCODONE/ IBUPROFEN						156	572,899,635	9,189,056,395	1,222,701,575
HYDROGESIC	Non	Non-Defendant	Non-Defendant	JAN1993	JAN2014	82	257,039	7,079,148	960,859
HYDROGESIC						82	257,039	7,079,148	960,859

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
HYDROMORPHONE	Def	Actavis	ACTAVIS	DEC2005	DEC2011	.	794,838	35,171,160	1,117,090
			RUGBY LABS	JAN1993	DEC1993	.	.	159,824	19,978
			WATSON LABS	JAN1994	DEC2000	.	.	85,688	10,711
		Dupont	ENDO LABS	FEB1997	JUL1997	.	62,920	1,035,288	74,902
		Endo Labs	ENDO LABS	AUG1997	FEB2014	.	4,907,812	319,772,784	24,216,896
			PAR PHARM	JAN1993	MAR2014	.	412,117	23,568	1,763
			QUALITEST PRODUCTS	JAN1993	DEC2011	.	800,355	101,453,656	8,086,469
			VINTAGE PHARM	APR1996	SEP2011	.	524,198	25,584,616	1,918,320
		Mallinckrodt	MALLINCKRODT	JUL1997	MAY2018	.	289,940,575	29,365,948,600	1,909,380,488
		Purdue	RHODES PHARM	JAN2010	MAY2018	.	131,000,937	9,108,887,124	539,808,777
		Teva	IVAX	JAN1996	DEC2000	.	.	3,073,368	194,261
			TEVA	JAN1993	AUG2013	.	16,252	647,792	33,124
			ZENITH GOLDLINE	JAN1993	DEC1995	.	.	3,735,744	252,394
	Dist	AmerisourceBergen	AMERICAN HLTH PKG	JAN2011	MAY2018	.	3,468,070	2,136,608	212,586
		Cardinal	MAJOR PHARM	MAY1994	MAR1999	.	75	12,888	1,074
		McKesson	MCKESSON	OCT2016	MAY2018	.	588,292	445,216	33,511
	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	160	227,499,726	13,185,011,688	756,441,920
HYDROMORPHONE						160	660,016,167	52,153,185,612	3,241,804,264
HYDROMORPHONE ER	Def	Mallinckrodt	MALLINCKRODT	MAY2014	MAY2018	.	232,606,491	642,834,480	9,165,897
		Teva	TEVA	MAY2014	MAY2018	.	76,282,884	310,531,664	5,978,981
	Non	Non-Defendant	Non-Defendant	MAY2015	MAY2018	.	53,619,817	220,111,648	4,189,990
HYDROMORPHONE ER						.	362,509,192	1,173,477,792	19,334,868
HYDROSTAT	Non	Non-Defendant	Non-Defendant	OCT1993	FEB2002	.	132,138	4,992,752	400,162

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
HYDROSTAT						.	132,138	4,992,752	400,162
IBUDONE	Non	Non-Defendant	Non-Defendant	JAN2008	MAY2018	7,962	7,116,006	43,970,135	5,059,108
IBUDONE						7,962	7,116,006	43,970,135	5,059,108
KADIAN	Def	Actavis	ACTAVIS	JAN2003	DEC2012	28,274	1,497,080,153	13,317,246,820	263,225,005
			ALLERGAN	AUG1996	MAY2018	9,294	655,320,052	3,137,867,270	60,650,767
			PUREPAC	JAN1998	MAY2004	18,027	.	41,056,940	764,029
	Non	Non-Defendant	Non-Defendant	JUL1996	DEC2008	241,743	69,855,692	1,015,061,900	19,698,622
KADIAN						297,338	2,222,255,897	17,511,232,930	344,338,423
LAZANDA	Non	Non-Defendant	Non-Defendant	JAN2011	MAY2018	28,032	97,663,789	5,537,616	137,863
LAZANDA						28,032	97,663,789	5,537,616	137,863
LIQUICET	Def	Mallinckrodt	MALLINCKRODT	JAN2007	MAR2012	.	46,403	103,160	10,316
LIQUICET						.	46,403	103,160	10,316
LORCET	Def	Actavis	FOREST PHARM	JAN1993	DEC2008	355,667	243,741,129	7,319,232,103	847,440,000
	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	4,713	351,171,089	211,900,390	23,250,552
LORCET						360,380	594,912,218	7,531,132,493	870,690,552
LORPAC	Def	Actavis	FOREST PHARM	NOV1993	NOV1993	.	.	760	152
LORPAC						.	.	760	152

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
LORTAB	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	629,014	920,496,016	9,458,735,270	1,850,332,039
LORTAB						629,014	920,496,016	9,458,735,270	1,850,332,039
MAGNACET	Def	Mallinckrodt	MALLINCKRODT	FEB2007	OCT2009	16,143	.	.	.
	Non	Non-Defendant	Non-Defendant	JAN2007	MAR2017	2,035	16,804,419	69,793,710	5,284,062
MAGNACET						18,178	16,804,419	69,793,710	5,284,062
MARGESIC H	Non	Non-Defendant	Non-Defendant	JAN1993	DEC2011	1,193	651,816	11,567,215	2,313,443
MARGESIC H						1,193	651,816	11,567,215	2,313,443
MAXIDONE	Def	Actavis	ACTAVIS	JAN2008	DEC2011	.	351,648	2,225,360	222,536
			WATSON LABS	JAN2000	JUN2008	48,981	16,271,751	110,877,010	11,087,701
		Teva	TEVA	JAN2012	JUL2014	.	63,727	352,270	35,227
MAXIDONE						48,981	16,687,126	113,454,640	11,345,464
MEPERGAN	Non	Non-Defendant	Non-Defendant	JAN1993	AUG2015	169	35,626,496	251,735,760	50,347,152
MEPERGAN						169	35,626,496	251,735,760	50,347,152

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
MEPERIDINE	Def	Actavis	ACTAVIS	JAN2001	DEC2011	.	4,265,305	111,849,550	18,498,651
			AMIDE PHARMACEUT	NOV1999	DEC2000	.	139,900	217,545	30,909
			RUGBY LABS	JAN1993	DEC1993	.	.	31,760	4,749
			SCHEIN PHARM	JAN1993	DEC1996	.	.	7,643,035	1,320,773
			WATSON LABS	JAN1994	DEC2007	253	5,353,455	72,221,975	12,583,175
		Endo Labs	PAR PHARM	JAN1993	MAY2018	.	6,495,253	92,613,810	16,055,493
			QUALITEST PRODUCTS	JAN1993	DEC2011	.	2,156,415	51,632,125	9,032,176
		Mallinckrodt	MALLINCKRODT	JAN2000	MAY2015	.	3,375,380	50,056,250	8,780,148
		Teva	BARR LABS	JAN1993	DEC2003	.	26,981,091	511,335,365	87,871,368
			IVAX	JAN1996	DEC2000	.	.	764,145	118,268
			TEVA	JAN1993	MAY2018	.	43,485,645	716,956,210	122,680,567
			ZENITH GOLDLINE	JAN1993	DEC1995	.	.	8,055,305	1,378,394
	Dist	Cardinal	MAJOR PHARM	JAN1993	MAY2005	.	.	1,305,660	231,289
			PARMED PHARM	JAN1993	MAY2001	.	14,857	255,370	51,074
	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	30	32,740,835	379,195,045	90,409,633
MEPERIDINE						283	125,008,136	2,004,133,150	369,046,667
MEPERIDINE/PROMETH	Def	Actavis	ACTAVIS	JAN2001	SEP2011	.	1,492,697	27,295,290	5,459,058
			AMIDE PHARMACEUT	JAN2000	DEC2000	.	7,143	47,245	9,449
		Endo Labs	QUALITEST PRODUCTS	APR1993	DEC1995	.	.	32,940,555	6,588,111
			VINTAGE PHARM	SEP1993	DEC1995	.	.	176,665	35,333
		Teva	TEVA	SEP2012	SEP2012	.	.	75	15
	Non	Non-Defendant	Non-Defendant	APR1998	MAY2018	.	13,928,080	242,395,610	48,479,122
MEPERIDINE/PROMETH						.	15,427,920	302,855,440	60,571,088

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
MEPERITAB	Def	Endo Labs	QUALITEST PRODUCTS	JAN1996	DEC2010	.	9,352,935	147,823,135	25,588,372
MEPERITAB						.	9,352,935	147,823,135	25,588,372
MEPROZINE	Def	Endo Labs	PAR PHARM	APR1993	MAR2015	.	11,749,734	3,865	773
			QUALITEST PRODUCTS	JAN1996	DEC2011	.	33,208,187	670,881,975	134,176,395
			VINTAGE PHARM	JAN1996	DEC2012	.	358,010	9,768,510	1,953,702
MEPROZINE						.	45,315,931	680,654,350	136,130,870
MORPHINE SULFATE	Def	Actavis	ACTAVIS	JAN2011	DEC2011	.	11,739,077	21,615,200	427,276
			PAR PHARM	JAN2011	MAY2018	.	194,625,836	1,179,252,950	23,967,136
			WATSON LABS	JAN2002	DEC2006	.	14,220,472	862,308,820	19,160,059
		Endo Labs	ENDO LABS	NOV1998	MAY2018	.	929,275,391	50,277,392,615	1,159,603,491
			PAR PHARM	JAN2007	MAR2018	.	192,694,207	20,089,984,655	484,157,041
		Mallinckrodt	MALLINCKRODT	JAN2003	MAY2018	.	1,189,386,143	67,582,174,595	1,737,176,602
		Purdue	ABG LABORATORIES	JUL1994	DEC2010	.	42,411,784	1,045,157,179	22,165,389
			PURDUE	APR1993	NOV2017	4,816	.	.	.
			RHODES PHARM	JAN2011	MAY2018	.	790,320,216	46,337,605,130	1,170,098,384
		Teva	TEVA	JAN2005	MAY2018	.	408,900,241	3,659,198,935	78,572,273
	Dist	AmerisourceBergen	AMERICAN HLTH PKG	JAN2011	MAY2018	.	4,619,237	7,310,610	197,946
		Cardinal	MAJOR PHARM	MAR2017	MAY2018	.	1,192,687	216,880	5,417
		McKesson	MCKESSON	APR2017	MAY2018	.	374,843	273,765	11,530
	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	1,164	894,856,018	78,909,187,742	3,656,904,475
MORPHINE SULFATE						5,980	4,674,616,152	269,971,679,076	8,352,447,019
MORPHINE SULFATE IR	Non	Non-Defendant	Non-Defendant	JAN2001	DEC2002	9	3,133,974	482,284,965	21,806,017

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
MORPHINE SULFATE IR						9	3,133,974	482,284,965	21,806,017
MS-CONTIN	Def	Purdue	PURDUE	JAN1993	DEC2012	201,202	824,877,612	29,168,691,680	628,357,631
			RHODES PHARM	JAN1993	MAY2018	1,361	804,375,086	465,986,215	7,971,205
MS-CONTIN						202,563	1,629,252,698	29,634,677,895	636,328,836
MS/L	Non	Non-Defendant	Non-Defendant	FEB1994	FEB2008	.	287,859	580,952	290,476
MS/L						.	287,859	580,952	290,476
MS/S	Non	Non-Defendant	Non-Defendant	MAR1994	NOV2003	.	85,053	670,715	43,370
MS/S						.	85,053	670,715	43,370
MSIR	Def	Purdue	PURDUE	JAN1993	JAN2018	21,665	39,843,574	2,804,518,156	130,696,318
MSIR						21,665	39,843,574	2,804,518,156	130,696,318
NORCO	Def	Actavis	ACTAVIS	JAN2008	DEC2010	.	58,403,733	376,025,218	39,252,571
			ALLERGAN	MAR1997	MAY2018	2,101	191,898,475	740,289,105	78,434,013
			WATSON LABS	MAR1997	OCT2012	164,768	233,144,747	3,139,275,290	329,898,735
	Non	Non-Defendant	Non-Defendant	JUN1999	JUN1999	141	.	.	.
NORCO						167,010	483,446,955	4,255,589,613	447,585,319

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
NUCYNTA	Def	Janssen	CENTOCOR	JUN2011	MAY2012	1,198	.	.	.
			JANSSEN PHARM	JAN2009	DEC2012	228,102	120,298,723	1,357,113,800	49,486,214
			MCNEIL	MAY2010	JUL2012	7,826	.	.	.
			ORTHO PHARM	JUN2009	SEP2012	91,296	.	.	.
			PRICARA	JUN2009	NOV2012	332,595	.	.	.
	Non	Non-Defendant	Non-Defendant	JAN2011	MAY2018	142,877	1,444,011,528	10,482,406,650	362,975,107
NUCYNTA						803,894	1,564,310,251	11,839,520,450	412,461,321
NUCYNTA ER	Def	Janssen	JANSSEN PHARM	SEP2011	DEC2012	97,585	.	.	.
			ORTHO PHARM	SEP2011	NOV2011	934	.	.	.
			PRICARA	AUG2011	JUL2012	12,642	.	.	.
	Non	Non-Defendant	Non-Defendant	JAN2011	MAY2018	100,069	981,605,812	5,712,869,640	110,541,964
NUCYNTA ER						211,230	981,605,812	5,712,869,640	110,541,964
NUMORPHAN	Def	Dupont	DUPONT PHARM	FEB1996	MAR1997	828	.	.	.
			ENDO LABS	JAN1993	JUL1997	.	1,225,383	3,237,195	215,813
		Endo Labs	ENDO LABS	AUG1997	MAR2007	214	577,684	1,212,225	80,815
NUMORPHAN						1,042	1,803,067	4,449,420	296,628
OMS	Non	Non-Defendant	Non-Defendant	JAN1993	JUN2002	.	593,090	22,853,960	1,142,698
OMS						.	593,090	22,853,960	1,142,698

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
ONCET	Def	Teva	IVAX	JAN1993	FEB1999	.	66,205	5,535	1,107
	Non	Non-Defendant	Non-Defendant	JAN1993	DEC1996	706	.	960,655	192,131
ONCET						706	66,205	966,190	193,238
ONSOLIS	Non	Non-Defendant	Non-Defendant	JAN2009	APR2018	7,423	393,120	51,336	907
ONSOLIS						7,423	393,120	51,336	907
OPANA	Def	Endo Labs	ENDO LABS	JAN2006	MAY2018	154,176	250,318,418	1,525,032,630	61,559,984
OPANA						154,176	250,318,418	1,525,032,630	61,559,984
OPANA ER	Def	Endo Labs	ENDO LABS	JAN2006	MAY2018	318,136	3,576,884,988	32,879,291,498	457,491,761
OPANA ER						318,136	3,576,884,988	32,879,291,498	457,491,761
OPIUM	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	.	208,291,410	917,339,580	91,733,958
OPIUM						.	208,291,410	917,339,580	91,733,958
ORALET	Non	Non-Defendant	Non-Defendant	MAR1995	DEC2006	5,227	1,137,251	72,813	3,047
ORALET						5,227	1,137,251	72,813	3,047
ORAMORPH SR	Non	Non-Defendant	Non-Defendant	JAN1993	JUL2016	75,090	279,428,522	6,427,385,820	138,183,145
ORAMORPH SR						75,090	279,428,522	6,427,385,820	138,183,145

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
OXYCODONE	Def	Actavis	ACTAVIS	JAN2001	DEC2011	14	507,208,403	50,115,964,883	1,575,499,165
			AMIDE PHARMACEUT	SEP1997	DEC2000	.	525,738	31,943,850	4,259,180
			WATSON LABS	AUG1999	MAR2007	113	10,845	312,435	41,658
		Endo Labs	PAR PHARM	SEP1998	MAY2018	.	421,333,886	42,854,535,285	1,470,106,333
			QUALITEST PRODUCTS	MAY1998	DEC2011	.	152,950,578	16,058,669,400	617,445,106
		Mallinckrodt	MALLINCKRODT	NOV1997	MAY2018	.	1,190,888,671	98,478,786,945	5,037,652,009
		Purdue	RHODES PHARM	SEP2014	MAY2018	.	62,568,848	5,179,100,595	305,885,673
		Teva	TEVA	SEP1997	MAY2018	.	465,359,988	62,986,201,613	1,857,326,160
	Dist	AmerisourceBergen	AMERICAN HLTH PKG	JAN2009	MAY2018	.	34,038,119	26,922,788	1,466,628
		Cardinal	MAJOR PHARM	MAR2015	MAY2018	.	11,590,900	2,237,358	217,982
		McKesson	MCKESSON	OCT2015	MAY2018	.	3,719,896	1,373,798	120,178
	Non	Non-Defendant	Non-Defendant	APR1996	MAY2018	955	1,583,231,550	116,269,945,952	6,929,216,012
OXYCODONE						1,082	4,433,427,422	392,005,994,900	17,799,236,084
OXYCODONE ER	Def	Endo Labs	DAVA PHARM	JAN2005	DEC2008	.	291,114,419	4,525,269,450	89,462,968
			ENDO LABS	JAN2005	MAY2013	.	371,810,112	10,199,579,880	265,939,473
			QUALITEST PRODUCTS	JAN2009	DEC2011	.	21,000,687	366,731,280	6,899,534
		Mallinckrodt	MALLINCKRODT	JAN2008	FEB2017	.	342,203,488	6,333,365,985	105,097,110
		Purdue	ACTAVIS	JAN2008	DEC2011	.	144,583,072	2,447,185,050	53,352,738
			APOTEX CORP	JAN2010	DEC2012	.	97,463,866	1,243,081,185	21,595,190
			ETHEX LABS	JAN2009	MAR2016	.	253,144,734	3,271,623,330	56,223,384
			IMPAX	DEC2015	MAY2018	.	41,675,163	262,646,055	5,201,895
			PAR PHARM	JAN2012	MAY2018	.	64,129,766	514,181,955	11,795,154
			RANBAXY PHARM	JAN2010	MAY2018	.	106,083,581	1,630,495,410	27,042,054
			SANDOZ	OCT2014	MAY2018	.	110,247,959	653,108,595	12,688,114

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
OXYCODONE ER	Def	Purdue	TEVA	JAN2004	MAY2018	16	2,281,930,095	40,138,571,775	661,185,544
			WATSON LABS	JAN2005	DEC2007	.	451,844,796	12,975,399,240	254,288,879
	Non	Non-Defendant	Non-Defendant	JAN2005	APR2018	.	17,521,960	312,158,400	2,628,815
OXYCODONE ER						16	4,594,753,698	84,873,397,590	1,573,400,852
OXYCODONE/APAP	Def	Actavis	ACTAVIS	JAN2001	DEC2011	.	599,606,420	34,917,550,823	2,979,290,638
			AMIDE PHARMACEUT	AUG1999	DEC2000	.	23,844	893,843	119,179
			PUREPAC	JAN1993	NOV2000	.	.	481,050	64,140
			RUGBY LABS	JAN1993	DEC1993	.	.	106,137,960	14,151,728
			SCHEIN PHARM	JAN1993	DEC1996	.	.	559,673,535	74,623,138
			WATSON LABS	JAN1994	DEC2007	.	437,968,839	12,849,660,214	1,106,092,510
		Endo Labs	ENDO LABS	JAN2000	FEB2008	.	90,257	4,530,743	604,099
			PAR PHARM	JAN1993	MAY2018	.	255,421,549	8,254,111,624	896,269,092
			QUALITEST PRODUCTS	JAN1993	DEC2011	.	16,363,741	3,438,067,148	458,408,953
			VINTAGE PHARM	JUN1997	FEB2011	.	829,889	20,689,268	2,758,569
		Mallinckrodt	MALLINCKRODT	JAN1993	MAY2018	515	1,871,591,368	97,887,541,249	10,827,770,572
		Purdue	RHODES PHARM	OCT2014	MAY2018	.	196,810,476	11,427,110,569	969,665,364
		Teva	BARR LABS	JAN1993	DEC2003	.	10,201,871	951,209,220	126,827,896
			IVAX	JAN1996	DEC2000	.	677,989	318,472,035	42,462,938
			TEVA	JAN1993	MAY2018	.	714,219,792	46,883,424,120	3,962,059,328
			ZENITH GOLDLINE	JAN1993	DEC1995	.	.	426,608,693	56,881,159

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
OXYCODONE/APAP	Dist	AmerisourceBergen	AMERICAN HLTH PKG	JAN2009	MAY2018	.	25,103,137	8,838,124	810,273
		Cardinal	MAJOR PHARM	JAN1993	MAY2018	.	8,248,703	84,673,661	11,180,570
			PARMED PHARM	JAN1993	MAY2004	.	881,005	46,235,678	6,164,757
		McKesson	MCKESSON	MAY2016	MAY2018	.	1,376,969	1,845,071	126,586
	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	.	1,617,357,920	53,548,860,221	4,449,613,183
OXYCODONE/APAP						515	5,756,773,769	271,736,614,845	25,985,944,672
OXYCODONE/ASA	Def	Actavis	ACTAVIS	JAN2008	DEC2011	.	16,688,606	173,173,859	23,657,631
			PUREPAC	APR1995	JUN1996	.	.	43,312	5,917
			RUGBY LABS	JAN1993	DEC1993	.	.	4,506,390	615,627
			SCHEIN PHARM	JAN1993	DEC1996	.	.	11,716,546	1,600,621
			WATSON LABS	JAN1994	DEC2007	.	23,242,491	333,538,962	45,565,432
		Endo Labs	PAR PHARM	JAN1993	DEC1993	.	8,301	.	.
			QUALITEST PRODUCTS	JAN1993	JUN2002	.	.	862,274	117,797
		Teva	BARR LABS	JAN1993	SEP2003	.	.	20,364,474	2,782,032
			IVAX	JAN1996	DEC2000	.	.	7,158,126	977,886
			TEVA	JAN1993	MAY2018	.	6,280,274	64,880,047	8,708,056
			ZENITH GOLDLINE	JAN1993	DEC1995	.	.	20,989,705	2,867,446
	Dist	Cardinal	MAJOR PHARM	JAN1993	JUL2001	.	.	3,545,881	484,410
			PARMED PHARM	JAN1993	JUN2010	.	340	732,366	100,050
	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	.	3,870,535	82,761,707	11,182,669
OXYCODONE/ASA						.	50,090,547	724,273,649	98,665,574

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
OXYCODONE/IBUPROF	Def	Actavis	ACTAVIS	JAN2008	DEC2011	.	1,938,729	17,167,425	2,288,990
			WATSON LABS	JAN2007	DEC2007	.	441,748	153,660	20,488
		Teva	TEVA	JAN2007	MAY2018	.	2,006,234	12,736,635	1,698,218
OXYCODONE/IBUPROF						.	4,386,711	30,057,720	4,007,696
OXYCONTIN	Def	Purdue	PURDUE	DEC1995	MAY2018	1,858,656	37,764,087,426	376,515,274,808	7,184,085,949
	Non	Non-Defendant	Non-Defendant	FEB1996	MAY2004	79,508	.	.	.
OXYCONTIN						1,938,164	37,764,087,426	376,515,274,808	7,184,085,949
OXYFAST	Def	Purdue	PURDUE	OCT1998	JAN2015	21,946	29,703,509	609,493,320	20,316,444
OXYFAST						21,946	29,703,509	609,493,320	20,316,444
OXYIR	Def	Purdue	PURDUE	JAN1996	JUL2016	51,246	47,613,176	1,168,757,550	155,834,340
OXYIR						51,246	47,613,176	1,168,757,550	155,834,340
OXYMORPHONE	Def	Endo Labs	ENDO LABS	JAN2010	MAY2018	.	79,180,157	658,409,445	25,775,281
			TEVA	APR2013	MAY2018	.	41,894,972	505,197,075	19,039,396
		Mallinckrodt	MALLINCKRODT	JUL2013	MAY2018	.	11,938,515	175,433,415	6,751,452
	Dist	AmerisourceBergen	AMERICAN HLTH PKG	JAN2016	JAN2018	.	23,810	8,880	296
	Non	Non-Defendant	Non-Defendant	JAN2010	MAY2018	.	264,983,547	2,355,525,960	90,095,517
OXYMORPHONE						.	398,021,001	3,694,574,775	141,661,942

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
OXYMORPHONE ER	Def	Actavis	ACTAVIS	JAN2011	MAR2012	1,143	3,565,221	16,132,793	402,258
		Teva	TEVA	JAN2012	MAY2018	422	123,160,315	1,361,177,205	26,215,548
	Non	Non-Defendant	Non-Defendant	JAN2013	MAY2018	.	652,626,753	6,996,966,330	102,302,785
OXYMORPHONE ER						1,565	779,352,289	8,374,276,328	128,920,591
PALLADONE	Def	Purdue	PURDUE	OCT2004	JUL2009	22,143	20,156,318	74,778,736	953,345
PALLADONE						22,143	20,156,318	74,778,736	953,345
PANLOR	Def	Purdue	PURDUE	JAN1993	DEC1993	2,613	.	1,796,990	359,398
	Non	Non-Defendant	Non-Defendant	JAN1993	MAR2018	35,084	200,265	4,061,680	812,336
PANLOR						37,697	200,265	5,858,670	1,171,734
PERCOCET	Def	Dupont	ENDO LABS	JAN1993	JUL1997	9,961	210,388,004	2,530,028,235	337,337,098
		Endo Labs	ENDO LABS	AUG1997	MAY2018	153,336	2,628,093,020	12,285,700,538	1,118,398,412
PERCOCET						163,297	2,838,481,024	14,815,728,773	1,455,735,510
PERCODAN	Def	Dupont	ENDO LABS	JAN1993	JUL1997	6,034	51,239,089	562,334,068	76,821,594
		Endo Labs	ENDO LABS	AUG1997	JAN2017	3,263	63,612,357	445,034,677	60,865,336
PERCODAN						9,297	114,851,446	1,007,368,745	137,686,930

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
PERCODAN-DEMI	Def	Dupont	ENDO LABS	JAN1993	JUL1997	.	670,601	2,483,087	678,439
		Endo Labs	ENDO LABS	AUG1997	DEC2005	.	315,944	584,308	159,647
PERCODAN-DEMI						.	986,545	3,067,395	838,086
PERCOLONE	Def	Endo Labs	ENDO LABS	NOV1997	AUG2007	8,834	1,468,205	4,522,335	602,978
PERCOLONE						8,834	1,468,205	4,522,335	602,978
PERLOXX	Non	Non-Defendant	Non-Defendant	JAN2006	JAN2011	1,745	582,600	3,360,315	277,709
PERLOXX						1,745	582,600	3,360,315	277,709
POLYGESIC	Def	Dupont	DUPONT PHARM	JAN1993	AUG1993	.	30,753	.	.
	Non	Non-Defendant	Non-Defendant	SEP1993	MAY2013	198	175,466	1,617,375	323,475
POLYGESIC						198	206,219	1,617,375	323,475
PRIMLEV	Non	Non-Defendant	Non-Defendant	JAN2008	MAY2018	14,273	21,641,372	51,702,285	3,905,268
PRIMLEV						14,273	21,641,372	51,702,285	3,905,268
PROCET	Def	Actavis	ACTAVIS	APR2008	JUL2011	.	.	2,940	392
			WATSON LABS	JAN2001	APR2009	170	998,441	2,362,113	331,916
PROCET						170	998,441	2,365,053	332,308
R.M.S.	Non	Non-Defendant	Non-Defendant	JAN1993	MAR2013	.	5,704,804	49,402,155	3,459,628
R.M.S.						.	5,704,804	49,402,155	3,459,628

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
REPREXAIN	Def	Actavis	ACTAVIS	JAN2008	DEC2011	206	51	46,950	9,390
			WATSON LABS	JAN2004	DEC2007	23,554	2,940,943	7,025,945	1,405,189
		Teva	TEVA	FEB2012	MAY2013	.	.	2,510	502
	Non	Non-Defendant	Non-Defendant	JAN2007	APR2018	40,930	25,028,667	140,840,058	16,169,734
REPREXAIN						64,690	27,969,661	147,915,463	17,584,815
ROXANOL	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	13,261	96,772,601	4,748,817,805	237,525,933
ROXANOL						13,261	96,772,601	4,748,817,805	237,525,933
ROXICET	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	2,155	289,657,921	23,620,323,423	3,196,649,350
ROXICET						2,155	289,657,921	23,620,323,423	3,196,649,350
ROXICODONE	Def	Mallinckrodt	MALLINCKRODT	JAN1993	MAY2018	29	189,814,629	1,691,464,691	58,716,693
	Non	Non-Defendant	Non-Defendant	JAN1993	JUL2016	24,361	206,488,445	6,402,427,335	512,917,195
ROXICODONE						24,390	396,303,074	8,093,892,026	571,633,888
ROXILOX	Non	Non-Defendant	Non-Defendant	JAN1993	DEC1997	12	.	781,409,633	104,187,951
ROXILOX						12	.	781,409,633	104,187,951
ROXIPRIN	Non	Non-Defendant	Non-Defendant	JAN1993	APR2011	115	7,352,614	503,974,420	68,849,121
ROXIPRIN						115	7,352,614	503,974,420	68,849,121

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
STAGESIC	Non	Non-Defendant	Non-Defendant	JAN1993	FEB2016	8,009	2,603,406	67,230,120	12,865,034
STAGESIC						8,009	2,603,406	67,230,120	12,865,034
SUBSYS	Def	Insys Therapeutics	INSYS THERAPEUTICS	JAN2012	MAY2018	94,710	1,458,491,889	2,166,317,136	16,914,066
SUBSYS						94,710	1,458,491,889	2,166,317,136	16,914,066
TYLOX	Def	Janssen	MCNEIL	JAN1993	FEB2014	2,318	156,113,829	1,273,352,393	169,780,319
TYLOX						2,318	156,113,829	1,273,352,393	169,780,319
ULTRAGESIC	Non	Non-Defendant	Non-Defendant	JAN1993	JAN1997	186	11,010	1,819,890	363,978
ULTRAGESIC						186	11,010	1,819,890	363,978
VANACET	Non	Non-Defendant	Non-Defendant	JAN1993	NOV2009	1,494	204,505	5,507,295	1,101,459
VANACET						1,494	204,505	5,507,295	1,101,459
VICODIN	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	150,925	487,889,447	4,532,783,150	906,556,630
VICODIN						150,925	487,889,447	4,532,783,150	906,556,630
VICODIN ES	Non	Non-Defendant	Non-Defendant	JAN1993	MAY2018	108,112	641,982,430	7,691,299,598	1,025,506,613
VICODIN ES						108,112	641,982,430	7,691,299,598	1,025,506,613
VICODIN HP	Non	Non-Defendant	Non-Defendant	OCT1996	MAY2018	28,058	122,018,236	1,271,734,270	127,173,427
VICODIN HP						28,058	122,018,236	1,271,734,270	127,173,427

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
VICOPROFEN	Non	Non-Defendant	Non-Defendant	SEP1997	APR2018	491,701	524,154,478	3,563,056,050	475,074,140
VICOPROFEN						491,701	524,154,478	3,563,056,050	475,074,140
XARTEMIS XR	Def	Mallinckrodt	MALLINCKRODT	MAR2014	MAY2018	60,199	13,471,890	48,875,321	4,344,473
XARTEMIS XR						60,199	13,471,890	48,875,321	4,344,473
XODOL	Non	Non-Defendant	Non-Defendant	JAN2004	APR2018	73,588	51,903,206	313,404,350	33,347,048
XODOL						73,588	51,903,206	313,404,350	33,347,048
XOLOX	Non	Non-Defendant	Non-Defendant	JAN2009	JAN2014	9,251	2,344,872	16,341,330	1,089,422
XOLOX						9,251	2,344,872	16,341,330	1,089,422
XYLON	Non	Non-Defendant	Non-Defendant	JAN2015	NOV2017	.	.	1,708,120	170,812
XYLON						.	.	1,708,120	170,812
ZAMICET	Non	Non-Defendant	Non-Defendant	JAN2008	MAY2018	13,071	9,830,487	21,532,529	32,138,103
ZAMICET						13,071	9,830,487	21,532,529	32,138,103
ZOHYDRO ER	Non	Non-Defendant	Non-Defendant	FEB2014	MAY2018	100,577	147,782,177	416,196,180	17,125,590
ZOHYDRO ER						100,577	147,782,177	416,196,180	17,125,590
ZOLVIT	Non	Non-Defendant	Non-Defendant	JAN2010	MAR2016	3,584	1,051,186	2,641,468	3,942,489

Source: IQVIA NPA, IPA, ARCOS, CDC

ARCOS Opioid Drugs and Defendant Corporate Groupings
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Drug	Manufacturer			Sales Period		Promotion	Wholesale	Retail	
Drug	Status	Defendant	Manufacturer	Start	End	Contacts	\$Wholesale	MME	EU TRx
ZOLVIT						3,584	1,051,186	2,641,468	3,942,489
ZYDONE	Def	Dupont	ENDO LABS	JAN1993	JUL1997	.	2,524,224	34,293,770	6,858,754
		Endo Labs	ENDO LABS	AUG1997	JAN2017	125,605	62,188,952	838,579,320	96,745,680
ZYDONE						125,605	64,713,176	872,873,090	103,604,434
						10,463,360	123,393,683,492	3,017,253,917,778	200,101,299,542

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
Def	Actavis	ACTAVIS	ANEXSIA	JAN2008	SEP2011	.	52	78,423	14,126
			BANCAP-HC	JUL2009	JAN2010	.	.	1,055	211
			COMBUNOX	JAN2009	DEC2010	.	480,290	2,634,818	351,309
			FENTANYL	JAN2008	DEC2011	.	726,633,462	21,540,905,100	51,020,755
			FENTANYL CIT	JAN2008	DEC2008	.	136,958,508	652,622,542	5,939,218
			HYDROCODONE/APAP	JAN2008	DEC2011	.	1,094,222,377	97,933,365,828	12,569,926,878
			HYDROCODONE/IBUPROFEN	JAN2008	DEC2011	.	33,102,016	1,155,080,160	154,010,688
			HYDROMORPHONE	DEC2005	DEC2011	.	794,838	35,171,160	1,117,090
			KADIAN	JAN2003	DEC2012	28,274	1,497,080,153	13,317,246,820	263,225,005
			MAXIDONE	JAN2008	DEC2011	.	351,648	2,225,360	222,536
			MEPERIDINE	JAN2001	DEC2011	.	4,265,305	111,849,550	18,498,651
			MEPERIDINE/PROMETH	JAN2001	SEP2011	.	1,492,697	27,295,290	5,459,058
			MORPHINE SULFATE	JAN2011	DEC2011	.	11,739,077	21,615,200	427,276
			NORCO	JAN2008	DEC2010	.	58,403,733	376,025,218	39,252,571
			OXYCODONE	JAN2001	DEC2011	14	507,208,403	50,115,964,883	1,575,499,165
			OXYCODONE/APAP	JAN2001	DEC2011	.	599,606,420	34,917,550,823	2,979,290,638
			OXYCODONE/ASA	JAN2008	DEC2011	.	16,688,606	173,173,859	23,657,631
			OXYCODONE/IBUPROF	JAN2008	DEC2011	.	1,938,729	17,167,425	2,288,990
			OXYMORPHONE ER	JAN2011	MAR2012	1,143	3,565,221	16,132,793	402,258
			PROCET	APR2008	JUL2011	.	.	2,940	392
			REPREXAIN	JAN2008	DEC2011	206	51	46,950	9,390
		ALLERGAN	COMBUNOX	JAN2011	SEP2015	648	690	17,963	2,395
			KADIAN	AUG1996	MAY2018	9,294	655,320,052	3,137,867,270	60,650,767
			NORCO	MAR1997	MAY2018	2,101	191,898,475	740,289,105	78,434,013

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
Def	Actavis	AMIDE PHARMACEUT	MEPERIDINE	NOV1999	DEC2000	.	139,900	217,545	30,909
			MEPERIDINE/PROMETH	JAN2000	DEC2000	.	7,143	47,245	9,449
			OXYCODONE	SEP1997	DEC2000	.	525,738	31,943,850	4,259,180
			OXYCODONE/APAP	AUG1999	DEC2000	.	23,844	893,843	119,179
		ANDRX	ANEXSIA	DEC2001	SEP2003	55,246	.	.	.
		FOREST PHARM	BANCAP-HC	JAN1993	DEC2007	.	611,158	23,619,630	4,723,926
			COMBUNOX	DEC2004	OCT2012	177,656	21,567,126	93,944,355	12,525,914
			DURADYNE DHC	FEB1993	DEC1997	.	.	13,170	2,634
			HY-5	FEB1993	AUG1995	.	.	970	194
			LORCET	JAN1993	DEC2008	355,667	243,741,129	7,319,232,103	847,440,000
			LORPAC	NOV1993	NOV1993	.	.	760	152
		PAR PHARM	MORPHINE SULFATE	JAN2011	MAY2018	.	194,625,836	1,179,252,950	23,967,136
		PUREPAC	KADIAN	JAN1998	MAY2004	18,027	.	41,056,940	764,029
			OXYCODONE/APAP	JAN1993	NOV2000	.	.	481,050	64,140
			OXYCODONE/ASA	APR1995	JUN1996	.	.	43,312	5,917
		ROYCE LABS	HYDROCODONE/APAP	MAR1996	SEP2007	.	1,716,548	201,633,420	29,722,584
		RUGBY LABS	HYDROCODONE/APAP	JAN1993	DEC1993	.	.	241,093,140	42,670,981
			HYDROMORPHONE	JAN1993	DEC1993	.	.	159,824	19,978
			MEPERIDINE	JAN1993	DEC1993	.	.	31,760	4,749
			OXYCODONE/APAP	JAN1993	DEC1993	.	.	106,137,960	14,151,728
			OXYCODONE/ASA	JAN1993	DEC1993	.	.	4,506,390	615,627
		SCHEIN PHARM	HYDROCODONE/APAP	JAN1993	DEC1996	.	.	331,060,138	59,766,894
			MEPERIDINE	JAN1993	DEC1996	.	.	7,643,035	1,320,773
			OXYCODONE/APAP	JAN1993	DEC1996	.	.	559,673,535	74,623,138
			OXYCODONE/ASA	JAN1993	DEC1996	.	.	11,716,546	1,600,621
		WARNER-CHILCOTT	HYDROCODONE/APAP	JAN1993	DEC2008	.	1,668,276	2,198,325,548	346,524,029

Source: IQVIA NPA, IPA, ARCOS, CDC

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
Def	Actavis	WATSON LABS	ANEXSIA	JAN2001	DEC2007	.	8,693,102	63,687,260	9,564,942
			FENTANYL	JAN2007	DEC2007	.	25,377,965	669,635,460	1,552,013
			FENTANYL CIT	JAN2006	DEC2007	.	216,176,727	854,520,628	7,927,174
			HYDROCODONE/APAP	JAN1993	DEC2007	36	1,211,764,949	117,827,099,253	16,363,285,321
			HYDROCODONE/IBUPROFEN	JAN2004	DEC2007	120	35,930,725	246,295,695	32,839,426
			HYDROMORPHONE	JAN1994	DEC2000	.	.	85,688	10,711
			MAXIDONE	JAN2000	JUN2008	48,981	16,271,751	110,877,010	11,087,701
			MEPERIDINE	JAN1994	DEC2007	253	5,353,455	72,221,975	12,583,175
			MORPHINE SULFATE	JAN2002	DEC2006	.	14,220,472	862,308,820	19,160,059
			NORCO	MAR1997	OCT2012	164,768	233,144,747	3,139,275,290	329,898,735
			OXYCODONE	AUG1999	MAR2007	113	10,845	312,435	41,658
			OXYCODONE/APAP	JAN1994	DEC2007	.	437,968,839	12,849,660,214	1,106,092,510
			OXYCODONE/ASA	JAN1994	DEC2007	.	23,242,491	333,538,962	45,565,432
			OXYCODONE/IBUPROF	JAN2007	DEC2007	.	441,748	153,660	20,488
			PROCET	JAN2001	APR2009	170	998,441	2,362,113	331,916
			REPREXAIN	JAN2004	DEC2007	23,554	2,940,943	7,025,945	1,405,189
Def	Actavis					886,271	8,238,914,701	373,686,119,955	37,236,001,322
	Dupont	DUPONT PHARM	NUMORPHAN	FEB1996	MAR1997	828	.	.	.
			POLYGESIC	JAN1993	AUG1993	.	30,753	.	.
		ENDO LABS	ENDOCET	JUN1994	JUL1997	.	11,644,969	975,194,408	130,025,921
			ENDODAN	JUL1994	JUL1997	.	1,234,991	71,243,146	9,689,410
			HYDROCODONE/APAP	FEB1995	JUL1997	.	7,708,650	396,580,690	56,450,301
			HYDROMORPHONE	FEB1997	JUL1997	.	62,920	1,035,288	74,902
			NUMORPHAN	JAN1993	JUL1997	.	1,225,383	3,237,195	215,813

Source: IQVIA NPA, IPA, ARCOS, CDC

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
	Dupont	ENDO LABS	PERCOCET	JAN1993	JUL1997	9,961	210,388,004	2,530,028,235	337,337,098
			PERCODAN	JAN1993	JUL1997	6,034	51,239,089	562,334,068	76,821,594
			PERCODAN-DEMI	JAN1993	JUL1997	.	670,601	2,483,087	678,439
			ZYDONE	JAN1993	JUL1997	.	2,524,224	34,293,770	6,858,754
Def	Dupont					16,823	286,729,584	4,576,429,886	618,152,232
	Endo Labs	DAVA PHARM	FENTANYL	MAR2005	AUG2008	.	.	63,180	193
			OXYCODONE ER	JAN2005	DEC2008	.	291,114,419	4,525,269,450	89,462,968
		ENDO LABS	ENDOCET	AUG1997	MAY2018	971	1,638,620,287	53,350,714,725	4,510,312,737
			ENDOCODONE	JAN1999	SEP2011	.	194,865	23,996,168	3,199,489
			ENDODAN	AUG1997	MAR2018	.	24,005,462	753,469,755	103,006,862
			HYDROCODONE/APAP	AUG1997	DEC2011	.	3,141,064	378,708,598	56,749,051
			HYDROMORPHONE	AUG1997	FEB2014	.	4,907,812	319,772,784	24,216,896
			MORPHINE SULFATE	NOV1998	MAY2018	.	929,275,391	50,277,392,615	1,159,603,491
			NUMORPHAN	AUG1997	MAR2007	214	577,684	1,212,225	80,815
			OPANA	JAN2006	MAY2018	154,176	250,318,418	1,525,032,630	61,559,984
			OPANA ER	JAN2006	MAY2018	318,136	3,576,884,988	32,879,291,498	457,491,761
			OXYCODONE ER	JAN2005	MAY2013	.	371,810,112	10,199,579,880	265,939,473
			OXYCODONE/APAP	JAN2000	FEB2008	.	90,257	4,530,743	604,099
			OXYMORPHONE	JAN2010	MAY2018	.	79,180,157	658,409,445	25,775,281
			PERCOCET	AUG1997	MAY2018	153,336	2,628,093,020	12,285,700,538	1,118,398,412
			PERCODAN	AUG1997	JAN2017	3,263	63,612,357	445,034,677	60,865,336
			PERCODAN-DEMI	AUG1997	DEC2005	.	315,944	584,308	159,647
			PERCOLONE	NOV1997	AUG2007	8,834	1,468,205	4,522,335	602,978
			ZYDONE	AUG1997	JAN2017	125,605	62,188,952	838,579,320	96,745,680

Source: IQVIA NPA, IPA, ARCOS, CDC

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
	Endo Labs	PAR PHARM	CODEINE SULFATE	MAY2012	JAN2017	.	.	4,815	950
			FENTANYL	JAN2007	DEC2011	.	179,953,654	5,301,198,180	12,368,406
			FENTANYL CIT	JAN2011	MAY2018	.	95,166,994	673,742,732	5,999,216
			HYDROCODONE/APAP	JAN1993	MAY2018	.	2,039,282,198	79,399,814,123	10,668,318,591
			HYDROCODONE/IBUPROFEN	JAN2012	MAY2018	.	15,830,351	511,487,430	67,940,313
			HYDROMORPHONE	JAN1993	MAR2014	.	412,117	23,568	1,763
			MEPERIDINE	JAN1993	MAY2018	.	6,495,253	92,613,810	16,055,493
			MEPROZINE	APR1993	MAR2015	.	11,749,734	3,865	773
			MORPHINE SULFATE	JAN2007	MAR2018	.	192,694,207	20,089,984,655	484,157,041
			OXYCODONE	SEP1998	MAY2018	.	421,333,886	42,854,535,285	1,470,106,333
			OXYCODONE/APAP	JAN1993	MAY2018	.	255,421,549	8,254,111,624	896,269,092
			OXYCODONE/ASA	JAN1993	DEC1993	.	8,301	.	.
		QUALITEST PRODUCTS	CODEINE SULFATE	JAN2009	NOV2011	.	121,137	1,453,995	245,907
			HYDROCODONE/APAP	JAN1993	DEC2011	.	777,736,276	73,395,393,860	10,675,145,434
			HYDROCODONE/IBUPROFEN	JAN2006	DEC2011	.	11,540,416	283,733,198	37,831,093
			HYDROMORPHONE	JAN1993	DEC2011	.	800,355	101,453,656	8,086,469
			MEPERIDINE	JAN1993	DEC2011	.	2,156,415	51,632,125	9,032,176
			MEPERIDINE/PROMETH	APR1993	DEC1995	.	.	32,940,555	6,588,111
			MEPERITAB	JAN1996	DEC2010	.	9,352,935	147,823,135	25,588,372
			MEPROZINE	JAN1996	DEC2011	.	33,208,187	670,881,975	134,176,395
			OXYCODONE	MAY1998	DEC2011	.	152,950,578	16,058,669,400	617,445,106
			OXYCODONE ER	JAN2009	DEC2011	.	21,000,687	366,731,280	6,899,534
			OXYCODONE/APAP	JAN1993	DEC2011	.	16,363,741	3,438,067,148	458,408,953
			OXYCODONE/ASA	JAN1993	JUN2002	.	.	862,274	117,797
		TEVA	OXYMORPHONE	APR2013	MAY2018	.	41,894,972	505,197,075	19,039,396

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
	Endo Labs	VINTAGE PHARM	HYDROCODONE/APAP	OCT1993	NOV2012	.	3,424,268	474,312,115	59,240,455
			HYDROMORPHONE	APR1996	SEP2011	.	524,198	25,584,616	1,918,320
			MEPERIDINE/PROMETH	SEP1993	DEC1995	.	.	176,665	35,333
			MEPROZINE	JAN1996	DEC2012	.	358,010	9,768,510	1,953,702
			OXYCODONE/APAP	JUN1997	FEB2011	.	829,889	20,689,268	2,758,569
Def	Endo Labs					764,535	14,216,409,702	421,234,755,807	33,720,504,246
	Insys Therapeutics	INSYS THERAPEUTICS	SUBSYS	JAN2012	MAY2018	94,710	1,458,491,889	2,166,317,136	16,914,066
Def	Insys Therapeutics					94,710	1,458,491,889	2,166,317,136	16,914,066
	Janssen	ALZA	DURAGESIC	AUG1994	JUN2002	2,470	.	.	.
		CENTOCOR	NUCYNTA	JUN2011	MAY2012	1,198	.	.	.
		JANSSEN PHARM	DURAGESIC	JAN1993	MAY2018	713,327	9,362,870,201	128,864,615,292	308,569,180
			NUCYNTA	JAN2009	DEC2012	228,102	120,298,723	1,357,113,800	49,486,214
			NUCYNTA ER	SEP2011	DEC2012	97,585	.	.	.
		JOHNSON & JOHNSON	DURAGESIC	JAN2013	FEB2018	3,698	.	.	.
		MCNEIL	DURAGESIC	JAN2005	AUG2007	5,875	.	.	.
			NUCYNTA	MAY2010	JUL2012	7,826	.	.	.
			TYLOX	JAN1993	FEB2014	2,318	156,113,829	1,273,352,393	169,780,319
		ORTHO PHARM	DURAGESIC	SEP1995	OCT2007	23,422	.	.	.
			NUCYNTA	JUN2009	SEP2012	91,296	.	.	.
			NUCYNTA ER	SEP2011	NOV2011	934	.	.	.

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
	Janssen	PRICARA	DURAGESIC	JAN2006	JUL2010	5,721	.	.	.
			NUCYNTA	JUN2009	NOV2012	332,595	.	.	.
			NUCYNTA ER	AUG2011	JUL2012	12,642	.	.	.
Def	Janssen					1,529,009	9,639,282,753	131,495,081,485	527,835,713
	Mallinckrodt	MALLINCKRODT	ANEXSIA	JAN1993	JAN2013	1,732	28,900,145	451,095,329	62,672,981
			EXALGO	JAN2010	MAY2018	170,646	723,155,200	1,852,300,544	32,091,412
			FENTANYL	JAN2011	MAY2018	170	723,472,390	28,776,567,787	71,032,836
			FENTANYL CIT	JAN2010	MAY2018	.	258,602,303	1,501,307,106	12,752,357
			HYDROCODONE/APAP	JAN1995	MAY2018	115	3,222,031,117	273,429,589,382	39,610,441,036
			HYDROMORPHONE	JUL1997	MAY2018	.	289,940,575	29,365,948,600	1,909,380,488
			HYDROMORPHONE ER	MAY2014	MAY2018	.	232,606,491	642,834,480	9,165,897
			LIQUICET	JAN2007	MAR2012	.	46,403	103,160	10,316
			MAGNACET	FEB2007	OCT2009	16,143	.	.	.
			MEPERIDINE	JAN2000	MAY2015	.	3,375,380	50,056,250	8,780,148
			MORPHINE SULFATE	JAN2003	MAY2018	.	1,189,386,143	67,582,174,595	1,737,176,602
			OXYCODONE	NOV1997	MAY2018	.	1,190,888,671	98,478,786,945	5,037,652,009
			OXYCODONE ER	JAN2008	FEB2017	.	342,203,488	6,333,365,985	105,097,110
			OXYCODONE/APAP	JAN1993	MAY2018	515	1,871,591,368	97,887,541,249	10,827,770,572
			OXYMORPHONE	JUL2013	MAY2018	.	11,938,515	175,433,415	6,751,452
			ROXICODONE	JAN1993	MAY2018	29	189,814,629	1,691,464,691	58,716,693
			XARTEMIS XR	MAR2014	MAY2018	60,199	13,471,890	48,875,321	4,344,473
Def	Mallinckrodt					249,549	10,291,424,708	608,267,444,838	59,493,836,382

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
	Purdue	ABG LABORATORIES	MORPHINE SULFATE	JUL1994	DEC2010	.	42,411,784	1,045,157,179	22,165,389
		ACTAVIS	OXYCODONE ER	JAN2008	DEC2011	.	144,583,072	2,447,185,050	53,352,738
		APOTEX CORP	OXYCODONE ER	JAN2010	DEC2012	.	97,463,866	1,243,081,185	21,595,190
		ETHEX LABS	OXYCODONE ER	JAN2009	MAR2016	.	253,144,734	3,271,623,330	56,223,384
		IMPAX	OXYCODONE ER	DEC2015	MAY2018	.	41,675,163	262,646,055	5,201,895
		PAR PHARM	OXYCODONE ER	JAN2012	MAY2018	.	64,129,766	514,181,955	11,795,154
		PURDUE	BUTRANS	OCT2010	MAY2018	936,856	1,351,300,636	2,541,126,263	16,397,778
			DILAUDID	MAY1993	MAY2018	362	168,163,202	2,480,817,992	177,525,376
			MORPHINE SULFATE	APR1993	NOV2017	4,816	.	.	.
			MS-CONTIN	JAN1993	DEC2012	201,202	824,877,612	29,168,691,680	628,357,631
			MSIR	JAN1993	JAN2018	21,665	39,843,574	2,804,518,156	130,696,318
			OXYCONTIN	DEC1995	MAY2018	1,858,656	37,764,087,426	376,515,274,808	7,184,085,949
			OXYFAST	OCT1998	JAN2015	21,946	29,703,509	609,493,320	20,316,444
			OXYIR	JAN1996	JUL2016	51,246	47,613,176	1,168,757,550	155,834,340
			PALLADONE	OCT2004	JUL2009	22,143	20,156,318	74,778,736	953,345
			PANLOR	JAN1993	DEC1993	2,613	.	1,796,990	359,398
		RANBAXY PHARM	OXYCODONE ER	JAN2010	MAY2018	.	106,083,581	1,630,495,410	27,042,054
		RHODES PHARM	DILAUDID	JAN1993	MAY2018	1,428	137,436,945	436,751,916	22,838,408
			HYDROCODONE/APAP	MAY2016	MAY2018	.	8,927,847	582,668,383	73,565,982
			HYDROMORPHONE	JAN2010	MAY2018	.	131,000,937	9,108,887,124	539,808,777
			MORPHINE SULFATE	JAN2011	MAY2018	.	790,320,216	46,337,605,130	1,170,098,384
			MS-CONTIN	JAN1993	MAY2018	1,361	804,375,086	465,986,215	7,971,205
			OXYCODONE	SEP2014	MAY2018	.	62,568,848	5,179,100,595	305,885,673
			OXYCODONE/APAP	OCT2014	MAY2018	.	196,810,476	11,427,110,569	969,665,364
		SANDOZ	OXYCODONE ER	OCT2014	MAY2018	.	110,247,959	653,108,595	12,688,114
		TEVA	OXYCODONE ER	JAN2004	MAY2018	16	2,281,930,095	40,138,571,775	661,185,544

Source: IQVIA NPA, IPA, ARCOS, CDC

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
	Purdue	WATSON LABS	OXYCODONE ER	JAN2005	DEC2007	.	451,844,796	12,975,399,240	254,288,879
Def	Purdue					3,124,310	45,970,700,624	553,084,815,199	12,529,898,713
	Teva	ANESTA CORPORATION	ACTIQ	APR2000	FEB2001	7,793	.	.	.
		BARR LABS	HYDROCODONE/APAP	JAN1993	DEC2003	.	645,891	137,011,355	25,927,642
			MEPERIDINE	JAN1993	DEC2003	.	26,981,091	511,335,365	87,871,368
			OXYCODONE/APAP	JAN1993	DEC2003	.	10,201,871	951,209,220	126,827,896
			OXYCODONE/ASA	JAN1993	SEP2003	.	.	20,364,474	2,782,032
		CEPHALON INC	ACTIQ	JAN1999	NOV2011	103,920	1,266,719,433	10,586,953,572	101,912,783
			FENTORA	OCT2006	DEC2011	105,707	.	46,246,473	933,398
		IVAX	HYDROCODONE/APAP	JAN1996	DEC2000	.	889,858	885,375,913	150,468,023
			HYDROMORPHONE	JAN1996	DEC2000	.	.	3,073,368	194,261
			MEPERIDINE	JAN1996	DEC2000	.	.	764,145	118,268
			ONCET	JAN1993	FEB1999	.	66,205	5,535	1,107
			OXYCODONE/APAP	JAN1996	DEC2000	.	677,989	318,472,035	42,462,938
			OXYCODONE/ASA	JAN1996	DEC2000	.	.	7,158,126	977,886
		TEVA	ACTIQ	JAN2006	MAY2018	24,054	1,324,832,929	1,428,490,622	12,783,489
			ANEXSIA	JUN2012	NOV2013	.	.	1,720	344
			BANCAP-HC	JAN1993	DEC1998	.	3,378,863	.	.
			CODEINE	JUN1993	JUN1993	.	9,409	.	.
			DURADYNE DHC	JAN1993	MAR1994	.	316	.	.
			FENTANYL	JAN2008	MAY2018	242	529,669,088	33,598,421,820	81,999,815
			FENTANYL CIT	JAN2006	MAY2018	.	991,273,039	5,503,421,300	49,731,436
			FENTORA	JAN2006	MAY2018	124,302	1,913,756,525	2,482,380,017	38,894,228
			HYDROCODONE/APAP	JAN1993	MAY2018	.	1,643,030,760	92,879,713,393	11,573,714,596

Source: IQVIA NPA, IPA, ARCOS, CDC

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
	Teva	TEVA	HYDROCODONE/IBUPROFEN	JAN2003	MAY2018	36	258,058,296	4,745,683,020	632,757,736
			HYDROMORPHONE	JAN1993	AUG2013	.	16,252	647,792	33,124
			HYDROMORPHONE ER	MAY2014	MAY2018	.	76,282,884	310,531,664	5,978,981
			MAXIDONE	JAN2012	JUL2014	.	63,727	352,270	35,227
			MEPERIDINE	JAN1993	MAY2018	.	43,485,645	716,956,210	122,680,567
			MEPERIDINE/PROMETH	SEP2012	SEP2012	.	.	75	15
			MORPHINE SULFATE	JAN2005	MAY2018	.	408,900,241	3,659,198,935	78,572,273
			OXYCODONE	SEP1997	MAY2018	.	465,359,988	62,986,201,613	1,857,326,160
			OXYCODONE/APAP	JAN1993	MAY2018	.	714,219,792	46,883,424,120	3,962,059,328
			OXYCODONE/ASA	JAN1993	MAY2018	.	6,280,274	64,880,047	8,708,056
			OXYCODONE/IBUPROF	JAN2007	MAY2018	.	2,006,234	12,736,635	1,698,218
			OXYMORPHONE ER	JAN2012	MAY2018	422	123,160,315	1,361,177,205	26,215,548
			REPREXAIN	FEB2012	MAY2013	.	.	2,510	502
		ZENITH GOLDLINE	HYDROCODONE/APAP	JAN1993	DEC1995	.	.	1,185,518,178	216,135,738
			HYDROMORPHONE	JAN1993	DEC1995	.	.	3,735,744	252,394
			MEPERIDINE	JAN1993	DEC1995	.	.	8,055,305	1,378,394
			OXYCODONE/APAP	JAN1993	DEC1995	.	.	426,608,693	56,881,159
			OXYCODONE/ASA	JAN1993	DEC1995	.	.	20,989,705	2,867,446
Def	Teva					366,476	9,809,966,915	271,747,098,171	19,271,182,376

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
Dist	AmerisourceBergen	AMERICAN HLTH PKG	HYDROCODONE/APAP	JAN2002	MAY2018	.	33,326,592	8,037,783	1,294,557
			HYDROCODONE/IBUPROFEN	JAN2007	MAY2018	.	781,116	874,103	116,547
			HYDROMORPHONE	JAN2011	MAY2018	.	3,468,070	2,136,608	212,586
			MORPHINE SULFATE	JAN2011	MAY2018	.	4,619,237	7,310,610	197,946
			OXYCODONE	JAN2009	MAY2018	.	34,038,119	26,922,788	1,466,628
			OXYCODONE/APAP	JAN2009	MAY2018	.	25,103,137	8,838,124	810,273
			OXYMORPHONE	JAN2016	JAN2018	.	23,810	8,880	296
Dist	AmerisourceBergen					.	101,360,081	54,128,894	4,098,833
	Cardinal	MAJOR PHARM	HYDROCODONE/APAP	JAN1993	MAY2018	.	24,322,060	1,190,407,440	195,140,102
			HYDROMORPHONE	MAY1994	MAR1999	.	75	12,888	1,074
			MEPERIDINE	JAN1993	MAY2005	.	.	1,305,660	231,289
			MORPHINE SULFATE	MAR2017	MAY2018	.	1,192,687	216,880	5,417
			OXYCODONE	MAR2015	MAY2018	.	11,590,900	2,237,358	217,982
			OXYCODONE/APAP	JAN1993	MAY2018	.	8,248,703	84,673,661	11,180,570
			OXYCODONE/ASA	JAN1993	JUL2001	.	.	3,545,881	484,410
		PARMED PHARM	HYDROCODONE/APAP	JAN1993	JAN2009	.	401,763	59,581,670	11,916,334
			MEPERIDINE	JAN1993	MAY2001	.	14,857	255,370	51,074
			OXYCODONE/APAP	JAN1993	MAY2004	.	881,005	46,235,678	6,164,757
			OXYCODONE/ASA	JAN1993	JUN2010	.	340	732,366	100,050
Dist	Cardinal					.	46,652,390	1,389,204,852	225,493,059

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
	McKesson	MCKESSON	HYDROCODONE/APAP	JAN1999	MAY2018	.	24,532,033	42,860,838	7,698,442
			HYDROCODONE/IBUPROFEN	JAN2012	MAR2018	.	50,078	18,540	2,472
			HYDROMORPHONE	OCT2016	MAY2018	.	588,292	445,216	33,511
			MORPHINE SULFATE	APR2017	MAY2018	.	374,843	273,765	11,530
			OXYCODONE	OCT2015	MAY2018	.	3,719,896	1,373,798	120,178
			OXYCODONE/APAP	MAY2016	MAY2018	.	1,376,969	1,845,071	126,586
Dist	McKesson					.	30,642,111	46,817,227	7,992,719
Non	Non-Defendant	Non-Defendant	ABSTRAL	JAN2011	MAY2018	33,389	70,280,073	46,413,354	805,325
			ACTIQ	FEB1999	MAR2000	2,922	.	.	.
			ALOR	AUG1995	MAY2003	6,845	398,067	5,936,560	1,187,312
			ANEXSIA	JAN1993	NOV1995	145,990	.	.	.
			ANOLOR DH	JAN1993	FEB2003	.	140,485	10,938,155	2,187,631
			AVINZA	JAN2002	MAY2018	482,085	1,511,822,464	14,333,238,045	203,489,466
			CETA	AUG1994	NOV2005	603	33,707	1,353,735	270,747
			CO-GESIC	JAN1993	FEB2014	13,689	4,035,095	63,297,380	12,659,476
			CODEINE	JAN1993	SEP2013	.	266,536	8,126,838	1,405,695
			CODEINE PHOSPHATE	JAN1993	DEC2013	.	6,788,371	50,371,563	11,436,504
			CODEINE SULFATE	JAN1993	MAY2018	193	104,230,544	1,037,272,925	188,388,872
			DAMASON	JAN1993	APR2010	1,820	4,490,106	48,213,125	9,642,625
			DEMEROL	JAN1993	MAY2018	466	156,782,838	936,474,896	170,234,783
			DEMEROL/APAP	JAN1993	JUN2002	.	506	196,600	39,320
			DILAUDID	JAN1993	FEB2008	31,974	69,234,232	3,284,462,236	225,172,934
			DOLAGESIC	JAN1996	NOV2008	.	15,796	2,928,330	585,666
			DOLOREX FORTE	FEB2001	JUN2011	.	65	9,370	1,874

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
Non	Non-Defendant	Non-Defendant	EMBEDA	JAN2009	MAY2018	223,728	280,811,796	1,041,962,850	26,979,678
			ETH-OXYDOSE	JAN2001	FEB2016	.	37,171,282	1,582,677,030	52,755,901
			FENTANYL	JAN2005	MAY2018	8,433	7,304,664,880	210,563,739,511	551,905,751
			FENTANYL CIT	JUN2010	MAR2015	.	.	132,288	1,579
			HY-PHEN	JAN1993	MAR2011	.	885,455	22,272,075	4,454,415
			HYCET	JAN2004	MAY2018	11,895	15,125,032	32,074,668	64,149,336
			HYCOMED	JAN1994	JUN2001	200	61,759	1,448,595	284,785
			HYDROCET	JAN1993	FEB2015	11,304	3,216,320	75,448,855	15,089,771
			HYDROCODONE/APAP	JAN1993	MAY2018	7,149	1,088,686,933	52,267,668,976	9,001,363,887
			HYDROCODONE/IBUPROFEN	JUN2003	MAY2018	.	217,606,637	2,245,884,250	297,203,300
			HYDROGESIC	JAN1993	JAN2014	82	257,039	7,079,148	960,859
			HYDROMORPHONE	JAN1993	MAY2018	160	227,499,726	13,185,011,688	756,441,920
			HYDROMORPHONE ER	MAY2015	MAY2018	.	53,619,817	220,111,648	4,189,990
			HYDROSTAT	OCT1993	FEB2002	.	132,138	4,992,752	400,162
			IBUDONE	JAN2008	MAY2018	7,962	7,116,006	43,970,135	5,059,108
			KADIAN	JUL1996	DEC2008	241,743	69,855,692	1,015,061,900	19,698,622
			LAZANDA	JAN2011	MAY2018	28,032	97,663,789	5,537,616	137,863
			LORCET	JAN1993	MAY2018	4,713	351,171,089	211,900,390	23,250,552
			LORTAB	JAN1993	MAY2018	629,014	920,496,016	9,458,735,270	1,850,332,039
			MAGNACET	JAN2007	MAR2017	2,035	16,804,419	69,793,710	5,284,062
			MARGESIC H	JAN1993	DEC2011	1,193	651,816	11,567,215	2,313,443
			MEPERGAN	JAN1993	AUG2015	169	35,626,496	251,735,760	50,347,152
			MEPERIDINE	JAN1993	MAY2018	30	32,740,835	379,195,045	90,409,633
			MEPERIDINE/PROMETH	APR1998	MAY2018	.	13,928,080	242,395,610	48,479,122
			MORPHINE SULFATE	JAN1993	MAY2018	1,164	894,856,018	78,909,187,742	3,656,904,475
			MORPHINE SULFATE IR	JAN2001	DEC2002	9	3,133,974	482,284,965	21,806,017

Source: IQVIA NPA, IPA, ARCOS, CDC

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
Non	Non-Defendant	Non-Defendant	MS/L	FEB1994	FEB2008	.	287,859	580,952	290,476
			MS/S	MAR1994	NOV2003	.	85,053	670,715	43,370
			NORCO	JUN1999	JUN1999	141	.	.	.
			NUCYNTA	JAN2011	MAY2018	142,877	1,444,011,528	10,482,406,650	362,975,107
			NUCYNTA ER	JAN2011	MAY2018	100,069	981,605,812	5,712,869,640	110,541,964
			OMS	JAN1993	JUN2002	.	593,090	22,853,960	1,142,698
			ONCET	JAN1993	DEC1996	706	.	960,655	192,131
			ONSOLIS	JAN2009	APR2018	7,423	393,120	51,336	907
			OPIUM	JAN1993	MAY2018	.	208,291,410	917,339,580	91,733,958
			ORALET	MAR1995	DEC2006	5,227	1,137,251	72,813	3,047
			ORAMORPH SR	JAN1993	JUL2016	75,090	279,428,522	6,427,385,820	138,183,145
			OXYCODONE	APR1996	MAY2018	955	1,583,231,550	116,269,945,952	6,929,216,012
			OXYCODONE ER	JAN2005	APR2018	.	17,521,960	312,158,400	2,628,815
			OXYCODONE/APAP	JAN1993	MAY2018	.	1,617,357,920	53,548,860,221	4,449,613,183
			OXYCODONE/ASA	JAN1993	MAY2018	.	3,870,535	82,761,707	11,182,669
			OXYCONTIN	FEB1996	MAY2004	79,508	.	.	.
			OXYMORPHONE	JAN2010	MAY2018	.	264,983,547	2,355,525,960	90,095,517
			OXYMORPHONE ER	JAN2013	MAY2018	.	652,626,753	6,996,966,330	102,302,785
			PANLOR	JAN1993	MAR2018	35,084	200,265	4,061,680	812,336
			PERLOXX	JAN2006	JAN2011	1,745	582,600	3,360,315	277,709
			POLYGESIC	SEP1993	MAY2013	198	175,466	1,617,375	323,475
			PRIMLEV	JAN2008	MAY2018	14,273	21,641,372	51,702,285	3,905,268
			R.M.S.	JAN1993	MAR2013	.	5,704,804	49,402,155	3,459,628
			REPREXAIN	JAN2007	APR2018	40,930	25,028,667	140,840,058	16,169,734
			ROXANOL	JAN1993	MAY2018	13,261	96,772,601	4,748,817,805	237,525,933
			ROXICET	JAN1993	MAY2018	2,155	289,657,921	23,620,323,423	3,196,649,350

Source: IQVIA NPA, IPA, ARCOS, CDC

Defendant Corporate Groupings and ARCOS Opioid Drugs
Contacts, Wholesale Dollars, and Retail Extended Units and MMEs
1993-2018

Manufacturer			Drug	Sales Period		Promotion	Wholesale	Retail	
Status	Defendant	Manufacturer	Drug	Start	End	Contacts	\$Wholesale	MME	EU TRx
Non	Non-Defendant	Non-Defendant	ROXICODONE	JAN1993	JUL2016	24,361	206,488,445	6,402,427,335	512,917,195
			ROXILOX	JAN1993	DEC1997	12	.	781,409,633	104,187,951
			ROXIPRIN	JAN1993	APR2011	115	7,352,614	503,974,420	68,849,121
			STAGESIC	JAN1993	FEB2016	8,009	2,603,406	67,230,120	12,865,034
			ULTRAGESIC	JAN1993	JAN1997	186	11,010	1,819,890	363,978
			VANACET	JAN1993	NOV2009	1,494	204,505	5,507,295	1,101,459
			VICODIN	JAN1993	MAY2018	150,925	487,889,447	4,532,783,150	906,556,630
			VICODIN ES	JAN1993	MAY2018	108,112	641,982,430	7,691,299,598	1,025,506,613
			VICODIN HP	OCT1996	MAY2018	28,058	122,018,236	1,271,734,270	127,173,427
			VICOPROFEN	SEP1997	APR2018	491,701	524,154,478	3,563,056,050	475,074,140
			XODOL	JAN2004	APR2018	73,588	51,903,206	313,404,350	33,347,048
			XOLOX	JAN2009	JAN2014	9,251	2,344,872	16,341,330	1,089,422
			XYLON	JAN2015	NOV2017	.	.	1,708,120	170,812
			ZAMICET	JAN2008	MAY2018	13,071	9,830,487	21,532,529	32,138,103
			ZOHYDRO ER	FEB2014	MAY2018	100,577	147,782,177	416,196,180	17,125,590
			ZOLVIT	JAN2010	MAR2016	3,584	1,051,186	2,641,468	3,942,489
Non	Non-Defendant					3,431,677	23,303,108,034	649,505,704,327	36,449,389,881
						10,463,360	123,393,683,492	3,017,253,917,778	200,101,299,542

SCHEDULE 9

OPIOID CLASS REMS

I. STATUTORY AUTHORITY

a. FDAAA of 2007

1. Before 2007, FDA did not have the authority to require a sponsor to implement a risk management plan for its drug product. That changed with the enactment of the Food and Drug Administration Amendments Act of 2007 (“FDAAA”), that gave FDA the authority to require a Risk Mitigation and Evaluation Strategy (“REMS”) to address drug risks.¹ FDA can require REMS at the time of initial approval or after the drug is already on the market.² Failure to comply with REMS renders the drug misbranded and allows for imposition of civil penalties.³

b. REMS Elements

1. REMS program under the FDAAA may include:
 - Medication Guide or Patient Package Insert⁴
 - Communication Plan⁵, and
 - Elements to Assure Safe Use (“ETASU”) such as:
 - certification and/or specialized training of prescribers
 - certification of pharmacies or other dispensers
 - dispensing/administration only in certain health care settings e.g., hospitals
 - dispensing/administration only with evidence of safe-use conditions
 - requiring each patient to be subject to certain monitoring
 - enrollment of treated patients in registries.⁶
 - Implementation System
2. REMS program must include a timetable for submission of assessments.⁷

II. DEVELOPMENT OF ER/LA OPIOID CLASS REMS

- a. On **February 6, 2009**, the FDA notified manufacturers of ER/LA opioid analgesics (later known as the Industry Working Group (“IWG”)) that their products would require a REMS to ensure the benefits outweigh the risks and inviting them to participate in a meeting to discuss REMS design.⁸ The meeting between the FDA and IWG was held on **March 3, 2009** and included a presentation of FDA’s initial REMS proposal (see chart below).⁹
- b. Between **March 2009 and July 2010**, FDA continued to obtain stakeholder input on the development of a REMS for these products, opening a public docket for comments and holding several public meetings.¹⁰

¹ See 21 U.S.C. 355-1.

² *Id.*

³ See 21 U.S.C. 331(d); 21 U.S.C. 333.

⁴ See 21 U.S.C. 355-1(e)(2).

⁵ See 21 U.S.C. 355-1(e)(3).

⁶ See 21 U.S.C. 355-1(f)(3).

⁷ See 21 U.S.C. 355-1(d).

⁸ END00373370 (FDA Notice to Endo)

⁹ ENDO-CHI_LIT-00067304.

¹⁰ See END00077908 (Federal Registrar Notice and Request for Comment); <http://wayback.archive-it.org/7993/20170113151927/http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm189737.htm> (May 4-5, 2009 Stakeholder Meetings); <http://wayback.archive-it.org/7993/20170112130238/http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm211808.htm> (May 27-29, 2009 Public Meeting); <http://wayback.archive-it.org/7993/20170112130238/http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm211808.htm>

c. On **July 22-23, 2010**, the FDA convened a joint meeting of the Anesthetic and Life Support Drugs Advisory Committee (“ALSDAC”) and the Drug Safety and Risk Management Advisory Committee (“DSaRM”) to discuss FDA’s new proposal for a ER/LA opioid REMS (see chart below) and to solicit feedback from the advisory committees and public on the components of the proposal. IWG presented its REMS proposal to the FDA in advance of the advisory committee meeting and later posted it to the public docket. (see chart below)¹¹

i. **Committee Vote:** 25-10 (0 abstained) against FDA-proposed REMS. Majority of those who voted “No” thought the FDA proposal does not adequately address the problems of abuse and misuse of opioids, that it should include IR opioids that are of equal concern, and that the ETASUs need to be more robust, including pilot studies and mandatory educational training programs. Even the members that voted “Yes” acknowledged insufficiencies of FDA’s proposal but thought it’s a good start to capture data.

ii. **Stakeholder Comments**

1. **Scope:** If the REMS only applies to ER/LA opioids, there will be a shift in prescribing to IR products or other potentially less effective pain relievers.
2. **Prescriber Education:** Many comments supported prescriber education but comments were divided as to whether such education should be mandatory.
 - a. Include safe use, storage, and disposal of opioid medications, pain management, benefits and risks of opioid treatment.
 - b. If education is mandated, REMS certification should be linked to DEA registration to maximize participation, minimize cost, and streamline the prescription process.
3. **Prescriber Certification:** Individual prescriber enrollment and real time verification of prescriber training at pharmacy level could cause “opting out.” Consider linking certification to DEA registration or state requirements (e.g. state Medical Board Licensure).
4. **Patient Education and Certification:** Patient education is vital to the safe use of REMS drugs. A REMS that employs a patient registration system would be overly burdensome and create a stigma for pain patients that could adversely affect patient access to necessary medications.
5. **Program Evaluation:** It is critical to assess the effectiveness of the program and its impact on appropriate access to pain medications.
6. **Other:** Less restrictive elements should be implemented first to determine if they are effective in mitigating risk while preserving access.

FDA 3/3/09 Proposal ¹²	IWG Proposal ¹³	FDA 7/22/2010 Proposal ¹⁴
Goals		
“To ensure that 1) benefits of the drugs continue to outweigh their risks through, proper patient selection; minimizing the risk of OD, accidental &	To ensure that the benefits of ER opioids continue to outweigh their risks, by reducing the potential for abuse, misuse, overdose, and addiction from the legitimate medical	To “[r]educe serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of long-acting and extended-release opioids while

it.org/7993/20170112130250/http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm193499.htm (December 4, 2009 Stakeholder Meeting).

¹¹ <https://www.regulations.gov/document?D=FDA-2009-N-0143-1199>.

¹² See ENDO-CHI_LIT-00067304 at 17; EPI002506034 at 4; <http://wayback.archive-it.org/7993/20170114050448/http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM163675.pdf>.

¹³ See END00079957; <https://www.regulations.gov/document?D=FDA-2009-N-0143-1199>.

¹⁴ ENDO-OR-CID-01214108.

intentional; and minimizing the risk of abuse; and 2) prescribers, dispensers and patients are aware of and understand the risks and appropriate use of these products.”	<p>use by:</p> <ol style="list-style-type: none"> 1) educating HCPs on proper patient selection and management, including avoiding inappropriate use in patients who are not opioid-tolerant; 2) educating HCPs and patients on the risks from accidental exposure to these products in children and other persons for whom they are not prescribed; 3) providing access for prescribers, pharmacists, and patients to information about the appropriate use, risks, proper storage, and appropriate disposal; and 4) providing access for prescribers to receive particular training in the safe use of these products. 	maintaining patient access to these medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.”
Scope		
Only ER/LA opioids.	All opioids, including IR and non-oral formulations.	ER/LA opioids only.
Medication Guide or Patient Package Insert		
Medication Guide	A Medication Guide in 3 variations, for oral opioids,...and for methadone, with the appropriate version dispensed with each prescription of a covered drug.	Will include "class" language regarding the safe use of all opioids and may also include product specific information.
Communication Plan		
None	Letters to prescribers, pharmacies, state medical, nursing, and pharmacy licensing authorities, targeted medical, nursing, and pharmacy associations, DEA registrants, highlighting risks to make sure benefits outweigh risks “from legitimate medical use” of opioids. Prescribers will be instructed to discuss risks with patients and encourage patients to use the PMIS.	None
Prescriber Education		
<p>Prescriber education and certification</p> <ul style="list-style-type: none"> • Attestation by dispensers that they are familiar with educational materials, drug risks, and conditions for safe use • May reflect special training • Retraining and recertification occur periodically 	<ul style="list-style-type: none"> • IWG would ensure that training is available to healthcare providers who prescribe long-acting opioid analgesics. • “Healthcare providers who prescribe [opioids subject to the REMS] will be sent training materials or information on how to obtain them.” • Training materials would include information on appropriate patient selection, screening for at-risk patients, dosing and risks of addiction, misuse, abuse and overdose, and safe storage and 	<ul style="list-style-type: none"> • Sponsors would be required to develop an educational program to educate prescribers about appropriate patient selection, dosing, and patient monitoring. Prescribers would also be trained to counsel patients on the safe use, storage, and disposal of opioids. • Prescriber education is not mandatory but sponsors would be required to demonstrate that prescribers have been trained and that knowledge of appropriate use has improved

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	disposal	via surveys of the prescribing community.
Dispenser Education		
Training and certification <ul style="list-style-type: none"> • Attestation by dispensers that they are familiar with educational materials, drug risks, and conditions for safe use • May reflect special training • Retraining and recertification occur periodically 	None	None
Patient Education		
To be done by the prescriber by virtue of the physician-patient agreement ("PPA"). PPA <ul style="list-style-type: none"> • Obtained at time of first prescription • Renewed every 12 months • Kept in patient's chart documenting program elements 	Patient Medication Information Sheet (PMIS) and Patient-Prescriber Agreement to aid prescribers in counseling patients <ul style="list-style-type: none"> • Patient Medication Information Sheet (PMIS), which is an aid to prescribers in counseling patients about the safe use of and potential for abuse, misuse, overdose from, and addiction to of long-acting opioid analgesics • References to available sample Patient-Prescriber Agreements 	"Sponsors would also be required to provide patient education sheets for prescribers to use in their interactions with patients, and sponsors would be required to encourage the prescribers to use these sheets when counseling patients. The content of these patient education sheets would be FDA approved." No patient registries.
Implementation System		
<ul style="list-style-type: none"> • Database of all enrolled entities including prescribers, pharmacies, practitioners and healthcare settings • Plan to monitor and evaluate implementation of elements of the REMS by health-care providers, pharmacists, and other parties in the healthcare system and work to improve implementation of such elements."¹⁵ 	None	None
Assessment Plan		
The Medication Guide will be assessed to assure it meets readability and suitability requirements and will be tested for patient comprehension. Prescriber training will be assessed by tracking through the implementation system, attestation, and e-mail surveys	Timetable for Assessments 1st Assessment after 18 months 2nd Assessment after 3 years 3rd Assessment after 7 years	Assessments would include <ul style="list-style-type: none"> • the effectiveness of the program in reducing serious adverse outcomes from the misuse and abuse • the impact on appropriate access to pain medications Metrics will include process

¹⁵ ENDO-CHI_LIT-00067304 at 9.

Timetable for Assessments 18 months, 3 years, and 7 years		measures, measures of patient and prescriber knowledge, certain behaviors (such as nonmedical use of prescription opioids), adverse events (unintentional overdose, addiction, and deaths related to prescription opioids), and access to care.
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III. FINAL REMS REQUIREMENTS

- a. On **July 9, 2012**, FDA approved final ER/LA Opioid REMS with the final Education Blueprint with the following elements:¹⁶
- b. **Goal:** To reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.
- c. **Medication Guide:** a one-page document with consumer-friendly information on the safe use and disposal of the ER/LA opioids, includes class-wide and product specific information.
- d. **Elements to Assure Safe Use**
 1. **Prescriber Training:** application holders must ensure that REMS-compliant training, based upon the FDA Blueprint for Prescriber Education is available. The training is REMS-compliant if: 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the 3) it includes a knowledge assessment of all of the sections of the FDA Blueprint, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.
 - **Prescriber Training Performance Goals:** The application holders were required to ensure the REMS-compliant training was made available by accredited CE providers by March 1, 2013 with the following performance goals:
 - Within 2 years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of the 320,000 active prescribers in 2011) will have been trained
 - Within 3 years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of the 320,000 active prescribers in 2011) will have been trained
 - Within 4 years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60% of 320,000 active prescribers in 2011) will have been trained
 - **Education Blueprint** – REMS education must cover the following topics:
 - Assessing patients for treatment;
 - Initiating, modifying and discontinuing therapy;
 - Managing ongoing therapy;
 - Counseling patients and caregivers about the safe use;
 - General drug information; and
 - Product-specific information
 2. **Prescriber Letters:** application holders were required to send three prescriber letters to all DEA-registered prescribers who are registered to prescribe Schedule II and III drugs. The letter notified prescribers about the REMS, the availability and importance of taking the REMS-compliant training through accredited CE, as well as encouraging the use of the Patient Counseling Document (PCD).

¹⁶ END00253928.

3. **Professional Organization/Licensing Board Letters:** application holders were required to send two letters specified state licensing boards, associations of state licensing boards, and professional organizations notifying these organizations about the REMS, the availability and importance of taking the REMS-compliant training through accredited CE, as well as encouraging the use of the PCD.
4. **Patient Counseling Document (PCD):** this document is provided to prescribers to give to patients, helping prescribers to properly counsel patients on their responsibilities for using these medicines safely.
- e. **Assessment Plan:** assessments must be submitted to the FDA by the application holders at 6 months, 12 months after the initial approval date of the REMS, and annually thereafter. The plan includes 8 key assessment elements:
 - Element 1: Number of ER/LA opioid analgesic prescribers who completed REMS-compliant training
 - Element 2: Independent audit of the quality and content of the educational programs
 - Element 3: Results of prescriber surveys
 - Element 4: Result of patient surveys
 - Element 5: Surveillance studies - key safety outcomes
 - Element 6: Drug utilization patterns
 - Element 7: Changes in prescribing behavior
 - Element 8: Evaluation of patient access

IV. POST-MARKETING REQUIREMENTS

- a. On **September 10, 2013**, FDA notified sponsors of ER/LA opioids of 5 new post-marketing requirements (“PMRs”).¹⁷ FDA explained that, “[b]ased on . . . review of relevant literature, [it] has concluded that more data are needed regarding the serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of ER/LA opioid” Therefore, FDA has determined that sponsors must conduct studies to:
 1. **2064-1:** Estimate incidence of and risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain.
 2. **2065-2:** Validate measures of misuse, abuse, addiction, overdose, and death.
 3. **2065-3:** Validate coded medical terminologies used to identify misuse, abuse, addiction, overdose, and death.
 4. **2065-4:** Validate definitions of “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and addiction.
 5. **2065-5:** Evaluate and estimate the serious risk of developing hyperalgesia following use of ER/LA opioid analgesics for at least 1 year to treat chronic pain
- b. On **February 4, 2016**, FDA released the 5 PMRs announced on September 10, 2013 and replaced them with the following 11 new PMRs (10 post-marketing studies and one clinical trial) with more refined measures for assessing the known serious risks of misuse, abuse, addiction, overdose, and death.¹⁸
 1. **3033-1:** “A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.” The study should estimate incidence of and risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain.

¹⁷ <https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf>.

¹⁸ <https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM484415.pdf>.

2. **3033-2:** “An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records.”
3. **3033-3:** “A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.”
4. **3033-4:** “An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.”
5. **3033-5:** “An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioid analgesics for chronic pain.”
6. **3033-6:** “An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.”
7. **3033-7:** “An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.”
8. **3033-8:** “An observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.”
9. **3033-9:** “An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.”
10. **3033-10:** “An observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.”
11. **3033-11:** “Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy.”

V. REMS-COMPLIANCE/ASSESSMENTS

- a. **6-Month Assessment Report¹⁹ (July 9, 2012-November 9, 2012):** the first REMS Assessment Report included the following data:
 1. **Prescriber Letter** “was successfully delivered to 98.4% (1,299,888/1,321,019) of the targeted DEA registrants.”
 2. **REMS Website** was launched on July 23, 2012.
 3. **Professional Organization/Licensing Board Letter** disseminated with 100% success delivery rate.
 4. **Call Center:** sponsors launched a fully-functional Call Center on July 23, 2012.
 5. **Element 1:** sponsors have already received 81 applications for CE grants and are on target to have the first REMS-compliant CE available on March 1, 2013.
- b. **12-Month Assessment Report²⁰ (November 9, 2012-May 10, 2013):** the second REMS Assessment Report included the following data:

¹⁹ EPI000087194 at 33-34.

²⁰ ENDO-OPIOID_MDL-00353276.

1. **Prescriber Letter 2** was “sent to all 1,342,173 unique prescribers in the DEA list of Prescribers on the DEA master registration file.”
 2. **Professional Organization/Licensing Board Letter 2** was sent on January 24, 2013 to “326 professional organizations and healthcare professional licensing boards.” One was returned.
 3. **Call Center:** RPC requested permission to decommission the call center because 1) low volume of calls (10 call a week on average), and 2) 95.3% of the calls have been on issues covered by FAQ available on the REMS website.
 4. **Element 1:** The first REMS-compliant education was available on February 28, 2013.
 5. **Element 3a:** RPC conducted a Baseline Prescriber Survey (BPS) to assess prescriber knowledge and understanding of opioid risks and appropriate prescribing practices. The survey was conducted before REMS education became available so it can serve as a baseline for future assessments. Of the 605 prescribers surveyed, more than 80% provided correct answers to majority of survey questions, “indicating a reasonably high level of knowledge.
 - a. “In terms of awareness of REMS educational materials, 165 prescribers (27.3%) indicated they were aware of the DDRP Letter, and of those who were aware and acknowledged receipt of the letter, 115 prescribers (89. 8%) reported reading it. Approximately half of the survey respondents (N = 266, 44.0%) indicated they were aware of the Medication Guide. Of those, 188 (87.4%) respondents indicated that they read the Medication Guide for the opioid analgesic they prescribe. One-third of prescribers (N = 195, 32.2%) were aware of the PCD prior to taking the survey, and 97 prescribers (16%) were aware of the ER/LA Opioid Analgesics REMS website (www.er-la-opioidrems.com).”
- c. **24-Month Assessment Report**²¹ (May 11, 2013-May 9, 2014) the third REMS Assessment Report included the following data:
1. **Prescriber Letter 3** was sent out to 84,009 new DEA-registrants and 93.9% of the letters were delivered.
 2. **The PCD** was downloaded (in order to view you must download) 2,461 times, and the Spanish PCD has been downloaded 196 times. Additionally, 202 PCD orders were placed and successfully fulfilled representing 520 pads.”
 3. **Call Center** was modified to utilize IVRS.
 4. **Element 1:** Only 20,345 prescribers have completed the RPC-supported, REMS-compliant training as of February 28, 2014, making it likely that RPC won’t meet its first education performance goal (80,000 by March of 2015).
 5. **Element 2:** Of the 27 independent audits, 22 (82%) met all criteria for REMS-compliant education. 5 failed to prominently display financial disclosures but did not impact content. One did not meet expectations with respect to scope of evaluation.
 6. **Element 4:** The report concluded that “Patient Survey results indicate that the REMS requirement to make available a medication guide has been achieved, but use of the PCD can be improved.”
 7. **Elements 5-7:** surveillance, drug utilization and appropriate prescribing metrics data, showed generally positive trends, but these are not necessarily attributable to REMS because 1) trends began before REMS and 2) they may be affected by other efforts to stem the opioid epidemic.

²¹ The report concluded that “[o]verall the REMS assessments indicate substantial improvements in various indicators, including patient knowledge; misuse, abuse, and major medical outcomes including death; as well as prescribing behaviors, all while preserving access to valuable pain therapies,” but “[s]ince many interventions targeting opioid analgesics occurred during the time period of the REMS, the aforementioned effects cannot be attributed specifically to the REMS.”

8. **Element 8:** “There is no indication that the REMS is having a negative impact on access from results of patients and prescribers surveys.”

d. **36-Month Assessment Report**²² (March 1, 2014 - February 28, 2015) the fourth REMS Assessment Report included the following data:

1. **Prescriber Letters:** Letter 3 was sent to 104,404 new DEA registrants
2. **Patient Counseling Document was downloaded** over 20,000 times.
3. **Element 1:** A total of 36,568 ER/LA opioid analgesic prescribers have completed a REMS-compliant CE activity as of February 28, 2015, hitting less than 50% of its first performance goal.
4. **Element 2:** 100% of the audited CE activities successfully complied with the REMS requirements for full/accurate inclusion of the FDA Blueprint content and the requisite knowledge assessments; 9 activities had non-content-related observations.
5. **Elements 3 & 4:** Overall knowledge rates for most of the six areas of the FDA Blueprint were high for both prescribers and patients.
6. **Element 5:** Surveillance data suggested possible decreases in some of the adverse events of interest. But, decreases began before REMS implementation and in products not subject to a REMS. Surveillance sources utilized have significant limitations for evaluating program impact (e.g. convenience sampling).
7. **Elements 6&7:** Fewer prescriptions written by most medical specialties for opioids. But, drop in prescriptions started prior to full REMS implementation. And it’s not possible to determine if the reason is appropriate prescribing.
8. **Element 8:** Cannot tell from drug use and survey data whether the REMS has impacted patient access to ER/LA opioids.

e. **FDA Advisory Committee to Assess Opioid REMS**²³

1. The FDA convened a joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) to assess ER/LA Opioid REMS.
2. **Education Goals:** the RPC did make first REMS-compliant education available in time (February 28, 2013), but hit only 47% of its first performance goal (37,512 prescribers) and 41% of its second (66,219 prescribers) . It should be noted that to count toward the goal, the prescriber must 1) be DEA-registered to prescribe CII or CIII drugs and have written at least one ER/LA prescription in past year, and 2) complete and pass all components of training. If individuals that do not meet the first criteria are counted, RPC almost meets both goals, and if individuals not meeting either criteria are counted, it more than exceeds goals.
3. **Independent Audits:** REMS require an independent audit of at least 10% of the RPC-funded REMS-compliant training to evaluate whether it covers all elements of the Blueprint, the post-course knowledge assessment measures all sections of the Blueprint and is conducted in accordance with ACCME or appropriate accreditation standards. By May 2016, 10% of RPC-funded CE were audited and 69% met all criteria. The failure of the other 31% to meet criteria was primarily due to issues of disclosure financial relationships.
4. **Committee Discussion**
 - The goals for REMS prescriber education are not too high and, in fact, might be too low.

²² ENDO-OPIOID_MDL-00013141.

²³<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm486856.htm>

- Prescriber education had potential for effectiveness but RPC efforts to evaluate its effectiveness were poor.
 - It is unknown whether REMS had an impact on patient access, but likely not.
 - It is difficult to evaluate whether REMS meets its goals because of lack of data, but clearly it does not assure safe use of opioids since the opioid epidemic continues.
 - REMS is not burdensome on patient access or on the healthcare delivery system.
 - Committee liked the current Medication Guide and Patient Counseling Document, but was concerned that the actual use and delivery of the medication guide was lacking.
 - IR products should be subject to REMS.
 - Prescriber education should be mandatory to prescribe ER and IR opioids and it should be linked DEA registration or licensure. If that's not possible, FDA should use its REMS authority to make it mandatory
5. **Committee Vote:** The Committee unanimously voted that FDA should modify the existing REMS. Several members thought IR opioids should be added and training be made mandatory. Others suggested FDA improve content to the blueprint, and improve patient education. One committee member stated that additional restrictive elements to the REMS should be considered. There was also suggestions to improve the evaluation of the effectiveness of the REMS.

f. **48-Month Assessment Report²⁴ (March 1 2015-February 29, 2016)**

1. **Prescriber Letters:** Letter 3 was sent to 73,172 new DEA registrants and a total of 69,216 registrants were reached.
2. **PCD:** More than 16,600 PCDs being distributed during the reporting period.
3. **Element 1:** A total of 66,881 ER/LA opioid analgesic prescribers completed an accredited REMS-compliant CE course funded by the [RPC] and met the FDA 's 'completers' criteria by 29 February 2016." This is less than half of the 160,000 prescribers performance goal set for March 2016.
4. **Element 2:** "Since the launch of the first RPC-supported accredited REMS-compliant CE activity on 28 February 2013, 783 CE activities have been launched and 85 audits have been conducted as of 29 February 2016. 4 received observations, 3 failed to prominently display financial disclosure and did not impact content but 1 was content related. RPC is investigating it.
5. **Element 3a:** The results of the 48-month Prescriber Follow-up Survey demonstrated that prescribers of ER/LA opioids are knowledgeable about the risks and safe use criteria based on the six domains of the FDA Education Blueprint.
6. **Element 3b:** The Prescriber Long-term Evaluation Survey results demonstrated that more than 80% of prescribers completing a REMS-compliant CE activity for ER/LA opioids have a strong understanding regarding assessing patients for treatment, managing patient therapy, counseling patients prescribed ER/LA opioid analgesics, and of general information for ER/LA opioid analgesic products but their knowledge of dose selection and management and information specific to certain drugs was lower.
7. **Element 4:** In a sample of adult, survey-eligible ER/LA opioid users, patient knowledge of the safe use of these products was assessed. A large majority of respondents reported that they received, read, and understood the Medication Guide. A smaller proportion of respondents reported that they received, had a healthcare provider who referenced, and understood the PCD. Knowledge of safe use measured through the KAS was high; 86% of commercially-insured, 85% of Medicare-insured, and 78% of Medicaid-insured respondents had a KAS of at least 80%. The only general knowledge questions that less than 80% of respondents answered correctly concerned storing ER/LA opioid analgesics

²⁴ ENDO-OPIOID_MDL-00039722.

away from other household medications; the need to read the Medication Guide at each pharmacy dispensing; never splitting or crushing pills (oral product users only); and informing a healthcare provider of fever....

8. **Element 5:** The MTF survey provides demographic data and substance use data for a large portion of the US population. While there are certain limitations of the data collected, the results contained in the annual report serves as an influential public health source on demographics and trends in substance use. The most relevant trends are highlighted below.
 - Overall, data from 2015 show that there has been a decrease in lifetime, annual, and 30-day prevalence of narcotics other than heroin since 2012 for 12th graders.
 - A decline has been observed for lifetime and annual prevalence of narcotics other than heroin for college students.
 - The narcotics other than heroin mentioned most by the 12th graders as being used in the last year without doctor's orders have been hydrocodone, codeine, Vicodin, oxycodone, morphine, and tramadol; however, trends in use have been declining since 2012, with the exception of tramadol where a slight increase over the past year has been observed.
 - OxyContin and Vicodin use has seen a decline in prevalence across 8th, 10th and 12th graders since 2012. A general downward trend was also observed in the percentage of students reporting that it would be easy or very easy to get narcotics other than heroin from 2012 to 2015.
 - Despite fluctuations in 2013, college students reported an overall increase in annual use of OxyContin from 2012 to 2015, while annual Vicodin use decreased overall during the same time period. Perceived availability that getting a narcotic other than heroin would be fairly easy or easy to get has shown a downward trend since 2012 for all age groups between 18-30, with the exception of a slight increase in those reporting getting a narcotic other than heroin would be fairly easy or easy to get for those aged 27-30.
9. **Elements 6-8:** Overall, a significant decrease was observed in total ER/LA opioid analgesic prescription volume from Pre-Implementation to the Active Period based on IMS data. The proportion of non-tolerant patients who were inappropriately prescribed ER/LA opioid analgesics decreased between the Pre-Implementation and the Active Period ER/LA opioid analgesics prescription volume decreased significantly for medical specialists with less compelling reasons to prescribe ER/LA opioid analgesics.

VI. ADDITION OF IR OPIOIDS

- a. FDA invited all affected applicant holders to a meeting on January 25, 2017, to inform them of the Agency's intention to require a REMS for IR, ER, and LA opioid analgesics and to discuss strategies for developing an expanded REMS that includes all applicant holders.
- b. On **September 28, 2018**, FDA sent letters to manufacturers of IR opioids informing them that their products that are intended to be used in the outpatient setting will be subject to the same REMS requirements as the ER/LA opioid analgesics.²⁵

²⁵ <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620935.htm>.

SCHEDULE 10

Actiq and Fentora Approved TIRF REMS Documents

Date	Contents	Source
12/28/2011	<p>Initial Actiq and Fentora TIRF REMS</p> <p>Summary</p> <ul style="list-style-type: none"> • FDA Letters Approving Final TIRF REMS for Actiq and Fentora • Discusses the goals of the TIRF REMS program • Outlines the elements required under the TIRF REMS program • Discusses requirements for dispensing from certified pharmacies, including inpatient pharmacies • Outlines the implementation of the TIRF REMS system 	<p>TEVA_MDL_A_076769522 (Actiq)</p> <p>TEVA_MDL_A_07679384 (Fentora)</p>

TIRF REMS FDA Questions and Answers

Date	Contents	Bates/Source
12/28/2011	<p>FDA Questions and answers relating to TIRF REMS</p> <p>Summary</p> <ul style="list-style-type: none"> • FDA approved a single, shared system REMS for TIRF products on December 28, 2011. • TIRF medicines contain fentanyl. • This REMS, called the TIRF REMS Access program, consists of a restricted distribution program to reduce the risk of misuse, abuse, addiction, and overdose with TIRF medicines. The TIRF REMS Access program is the first approved class REMS for drugs in the opioid class. We are continuing work on another class REMS for the class of long-acting and extended-release opioids. • The current list of TIRF medicines include Abstral, Actiq, Fentora, Lazanda, and Onsolis. • Healthcare providers who prescribe transmucosal immediate-release fentanyl (TIRF) medicines for outpatient use are required to enroll in the TIRF REMS Access program. Healthcare providers who are already enrolled in an individual Risk Evaluation and Mitigation Strategy (REMS) program for at least 	FDA Website ¹

¹ <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm284717.htm>

	<p>one TIRF medicine will not need to re-enroll because they will be automatically transitioned to the shared TIRF REMS Access program. Prescribers will be required to re-enroll in the TIRF REMS program every two years from the date of enrollment into the TIRF class REMS or from the date of enrollment into the individual REMS, whichever was earlier.</p> <ul style="list-style-type: none"> Both outpatient and inpatient pharmacies that dispense transmucosal immediate-release fentanyl (TIRF) medicines are required to enroll in the TIRF REMS Access program. Pharmacies that were previously enrolled in an individual TIRF Risk Evaluation and Mitigation Strategy (REMS) will not need to re-enroll because they will be automatically transitioned to the shared TIRF REMS Access program. Pharmacies will be required to re-enroll in the TIRF REMS program every two years from the date of enrollment into the TIRF class REMS or from the date of enrollment into the individual REMS, whichever was earlier. Patients who are prescribed transmucosal immediate-release fentanyl (TIRF) medicines on an outpatient basis must sign a Patient-Prescriber Agreement with their healthcare provider and will be asked to read the Medication Guide provided to them by their prescriber. Patients can then take their prescription to an enrolled pharmacy. 	
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2017 TIRF REMS Document

Date	Contents	Source
08/2017	<p>Most recent TIRF REMS from FDA website.</p> <p>Summary</p> <ul style="list-style-type: none"> Discusses the goals of the TIRF REMS program Outlines the elements required under the TIRF REMS program Discusses requirements for dispensing from certified pharmacies, including inpatient pharmacies Outlines the implementation of the TIRF REMS system 	FDA Website ²

² https://www.accessdata.fda.gov/drugsatfda_docs/remes/TIRF_2017-09-07_Full.pdf

Approved TIRF REMS Opioid Products Chart

Date	Contents	Bates
N/A	<p>Chart from FDA website with approved TIRF REMS Opioid Products.</p> <p>Summary</p> <ul style="list-style-type: none">• Provides list of approved TIRF products subject to the TIRF REMS program:<ul style="list-style-type: none">○ Abstral○ Actiq○ Subsys○ Onsolis○ Lazanda○ Fentora○ Fentanyl Buccal (ANDA 079075)○ Fentanyl Citrate (ANDA 207338)○ Fentanyl Citrate (ANDA 078907)○ Fentanyl Citrate (ANDA 077312)	FDA Website ³

TIRF REMS Education Program for Prescribers and Pharmacists Document

Date	Contents	Source
N/A	<p>TIRF REMS Education Program for Prescribers and Pharmacist document from TIRF REMS website.</p> <p>Summary</p> <ul style="list-style-type: none">• Provides products covered under the TIRF REMS program, including approved generic equivalents.• Discussed the Education Program and enrollment procedures.• Outlines appropriate patient selection with reference to approved indication.• Notes specific patient risk factors, including risk of misuse, abuse, addiction, and overdose, accidental ingestion, and drug interactions.	FDA Website ⁴

³<https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemisDetails.page&REMS=60>⁴ https://www.accessdata.fda.gov/drugsatfda_docs/remis/TIRF_2017-09-07_Education_Program_for_Prescribers_and_Pharmacists.pdf

SCHEDULE 12

PURDUE
LABEL CHANGES FOR MS CONTIN
(NDA 19516)¹

SUMMARY OF LABEL CHANGES

The FDA approved MS Contin on May 29, 1987. A summary of label changes with regards to indications, abuse, addiction, and withdrawal is provided below, as well as a more in-depth review of the label changes.²

- In the **1996 Physicians' Desk Reference Label** the indication changed from the previous the 1993 Physician's Desk Reference Label to include, "[t]he MS CONTIN 200 mg Tablet strength is a high dose, controlled-release, oral morphine formulation indicated for the relief of pain in opioid treatment patients only."
- **May 11, 2010**
 - a) **Black Box Warning** for misuse, abuse, or diversion.
 - b) The indication changed in **Indications and Usage** to "MS CONTIN tablets are controlled-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."
 - c) A new section on **Misuse, Abuse and Diversion of Opioids** was added.
 - d) The **Drug Abuse and Addiction** section was substantially changed.
 - e) New sections on **Tolerance** and **Physical Dependence** were added.
 - f) Information on abuse was included in **Information for Patients/Caregivers**.
 - g) A new section on **Cessation of Therapy** was added.
- **July 9, 2012**
 - a) A **Highlights of Prescribing Information** section was added.
 - b) The **Boxed Warning** in the **Highlights of Prescribing Information** had the following language on abuse: "MS CONTIN contains morphine

¹ Source: Label Information, NDA 19516, available at <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=019516>; MS Contin. (1989). In *Physicians' Desk Reference* (43rd ed., pp. 1656-1658) Montvale, NJ: PDR Network; MS Contin (1990). In *Physicians' Desk Reference* (44th ed., pp. 1710-1713) Montvale, NJ: PDR Network; MS Contin (1991). In *Physicians' Desk Reference* (45th ed., pp. 1748-1750) Montvale, NJ: PDR Network; MS Contin (1990). MS Contin (1992) In *Physicians' Desk Reference* (46th ed., pp. 1814-816) Montvale, NJ: PDR Network; MS Contin (1993). In *Physicians' Desk Reference* (47th ed., pp. 1884-1886) Montvale, NJ: PDR Network; MS Contin (1996). In *Physicians' Desk Reference* (50th ed., pp. 1994-1997) Montvale, NJ: PDR Network; MS Contin (1997). In *Physicians' Desk Reference* (51st ed., pp. 2149-2152) Montvale, NJ: PDR Network; MS Contin (1998). In *Physicians' Desk Reference* (52nd ed., pp. 2330-2333) Montvale, NJ: PDR Network.

² All labels were not available for review. Labels from the Physicians' Desk Reference from 1989-1993 and 1996-1998 were reviewed as well as all labels available through the FDA.

sulfate, a Substance II controlled substance. Monitor for signs of misuse, abuse, and addiction during MS CONTIN therapy.”

- c) The **Boxed Warning** in the **Full Prescribing Information** section was changed.
- d) A new section **2.2 Titration and Maintenance** was added.
- e) A new section **2.3 Discontinuation of MS Contin** was added.
- f) A new section **2.4 Administration of MS Contin** was added.
- g) A new section **5.11 Avoidance of Withdrawal** was added.
- h) **Section 9.2 Abuse** underwent a substantial revision.
- i) A new **Section 9.3 Dependence** was added.
- **April 16, 2014**
 - a) The **Black Box Warning** in the **Highlights of Prescribing Information** changed the language on abuse to: “MS CONTIN exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk before prescribing, and monitor regularly for development of these behaviors and conditions.”
 - b) The indication in **Section 1 Indications and Usage** was changed to “MS CONTIN is an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.”
 - c) The limitations of use in **Section 1 Indications and Usage** was changed to include language on abuse.
 - d) The **Boxed Warning** in the **Full Prescribing Information** section was changed.
 - e) The language in **Section 2.2 Titration and Maintenance of Therapy** was substantially changed.
 - f) Addiction, Abuse and Misuse were added to **Section 6 Adverse Reactions**.
- **December 16, 2016**
 - a) Language on abuse was added to **Section 2.1 Dosage and Administration**.
 - b) **Section 2.3 Discontinuation of MS CONTIN** had a major revision to the language.
 - c) Withdrawal was added to **Section 6 Adverse Reactions**.

DETAILED REVIEW OF LABEL CHANGES

I. 1996 to 1998 Physicians' Desk Reference Labels

1. The indication changed in the **Indications and Usage** section.

1989-1993 PDR Indication	
<p>INDICATIONS AND USAGE</p> <p>MS CONTIN is a controlled-release oral morphine formulation indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days.</p>	
1996 to 1998 PDR Indication	
<p>MS CONTIN is a controlled-release oral morphine formulation indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days.</p> <p>The MS CONTIN 200 mg Tablet strength is a high dose, controlled-release, oral morphine formulation indicated for the relief of pain in opioid tolerant patients only.</p>	

III. May 11, 2010

- a) The **Black Box Warning** contains language on abuse.

MS CONTIN contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.

Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing MS CONTIN in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

MS CONTIN TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, DISSOLVED, OR CRUSHED. TAKING BROKEN, CHEWED, DISSOLVED, OR CRUSHED MS CONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

- b) The indication in **Indications and Usage** changed.

1998 PDR Label- Indication
<p>MS CONTIN is a controlled-release oral morphine formulation indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days.</p> <p>The MS CONTIN 200 mg Tablet strength is a high dose, controlled-release, oral morphine formulation indicated for the relief of pain in opioid tolerant patients only.</p>
5/2010 Revised Label - Indication
<p>MS CONTIN Tablets are a controlled-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.</p> <p>MS CONTIN Tablets are NOT intended for use as a prn analgesic.</p> <p>The MS CONTIN 100 and 200 mg tablet strengths are high dose, controlled-release, oral morphine formulations indicated for the relief of pain in opioid-tolerant patients only.</p> <p>MS CONTIN is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.</p> <p>MS CONTIN is not indicated for pain in the postoperative period if the pain is mild, or not expected to persist for an extended period of time.</p> <p>MS CONTIN is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)</p>

- c) A new section on **Misuse, Abuse and Diversion of Opioids** was added with the previous language completely removed.

5/2010 Revised Label
<p>Morphine is an opioid agonist and a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.</p>

Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing MS CONTIN[®] in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

MS CONTIN can be abused by crushing, chewing, snorting or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS: Drug Abuse and Addiction**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

- d) The section on **Drug Abuse and Addiction** was substantially changed.

5/2010 Revised Label

MS CONTIN is a mu-agonist opioid with an abuse liability similar to other opioid agonists and is a Schedule II controlled substance. MS CONTIN and other opioids used in analgesia, can be abused and are subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

“Drug-seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. MS CONTIN[®], like other opioids, has been diverted for non-medical use. Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

MS CONTIN is intended for oral use only as an intact tablet. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. Due to the presence of talc as one of the excipients in tablets, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

e) A section on **Tolerance** was added.

5/2010 Revised Label

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

f) A section on **Physical Dependence** was added.

5/2010 Revised Label

Physical dependence is a state of adaptation that is manifested by an opioid specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

g) A new section on **Information for Patients/Caregivers** was added.

5/2010 Revised Label

Patients should be advised that MS CONTIN[®] is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

h) A new section on **Cessation of Therapy** was added.

5/2010 Revised Label

When the patient no longer requires therapy with MS CONTIN[®] tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

IV. July 9, 2012

1. A new **Highlights of Prescribing Information** was added.
2. The **Boxed Warning** in the **Highlights of Prescribing Information** had the following language on abuse: “MS CONTIN contains morphine sulfate, a Substance II controlled substance. Monitor for signs of misuse, abuse, and addiction during MS CONTIN therapy.”
3. The **Boxed Warning** in the **Full Prescribing Information** section was changed.

5/2010 Revised Label – Boxed Warning

MS CONTIN contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.

Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing MS CONTIN in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

7/2012 Revised Label – Boxed Warning

Abuse Potential

MS CONTIN[®] contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit [see *Warnings and Precautions (5.1)*]. Assess each patient’s risk for opioid abuse or addiction prior to prescribing MS CONTIN. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving MS CONTIN for signs of misuse, abuse, and addiction during treatment [see *Drug Abuse and Dependence (9)*].

4. The following were added to the limitations of use in **Section 1 Indications and Usage**: “for pain that is mild or not expected to persist for an extended period of time” and “for acute pain.”
5. A new **Section 2.2 Titration and Maintenance** was added.

7/2012 Revised Label – Section 2.2 language added

Individually titrate MS CONTIN to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving MS CONTIN to assess the maintenance of pain control and the relative incidence of adverse reactions. During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), periodically reassess the continued need for the use of opioid analgesics.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the MS CONTIN dose to decrease the level of pain. Because steady-state plasma concentrations are approximated in 1 day, MS CONTIN dosage adjustments may be done every 1 to 2 days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid and non-opioid medication.

If signs of excessive opioid-related adverse reactions are observed, the next dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

During chronic, around-the-clock opioid therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

6. A new **Section 2.3 Discontinuation of MS Contin** was added.

7/2012 Revised Label – Section 2.3 language added

When the patient no longer requires therapy with MS CONTIN tablets, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue MS CONTIN.

7. A new section **2.4 Administration of MS Contin** was added.

7/2012 Revised Label – Section 2.4 language added

Instruct patients to swallow MS CONTIN tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of morphine [see *Warnings and Precautions (5.2)*].

8. The below language was added to **Section 5.1 Abuse Potential**.

7/2012 Revised Label – Section 5.1

Assess each patient's risk for opioid abuse or addiction prior to prescribing MS CONTIN. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

9. A new section **5.11 Avoidance of Withdrawal** was added.

7/2012 Revised Label – Section 5.11

Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including MS CONTIN. In these patients, mixed agonists/antagonists analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing MS CONTIN, gradually taper the dose [see *Dosage and Administration (2.3)*]. Do not abruptly discontinue MS CONTIN.

10. New subsections **9.1 Controlled Substance** and **9.2 Abuse** were added under **Drug Abuse and Dependence**.

11. The language in **9.1 Controlled Substance** was changed.

5/2010 Revised Label

MS CONTIN is a mu-agonist opioid with an abuse liability similar to other opioid agonists and is a Schedule II controlled substance. MS CONTIN and other opioids used in analgesia, can be abused and are subject to criminal diversion.

7/2012 Revised Label – Section 9.1

MS CONTIN contains morphine, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. MS CONTIN can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions (5.1)*].

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

12. The below language was added to **Section 9.2 Abuse**.

7/2012 Revised Label – Section 9.2 language added

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Risks Specific to Abuse of MS CONTIN

MS CONTIN is for oral use only. Abuse of MS CONTIN poses a risk of overdose and death. This risk is increased with concurrent abuse of MS CONTIN with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved MS CONTIN enhances drug release and increases the risk of over dose and death.

Due to the presence of talc as one of the excipients in MS CONTIN, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

13. The paragraph on drug addiction in **Section 9.2 Abuse** had a change in language.

5/2010 Revised Label

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

7/2012 Revised Label – Section 9.2 language changed

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

14. The language on “doctor shopping” in **Section 9.2 Abuse** was changed from “[d]octor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction” to “[d]octor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.”

15. In **Section 9.2 Abuse** the sentence “[i]n addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances” was shortened to “[i]n addition, abuse of opioids can occur in the absence of true addiction.”

16. A new **Section 9.3 Dependence** was added.

7/2012 Revised Label – Section 9.3 language added

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, , nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

MS CONTIN should not be abruptly discontinued [see *Dosage and Administration* (2.3)]. If MS CONTIN is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see *Use in Specific Populations* (8.6)].

17. The language in **Section 17 Patient Counseling Information** on abuse was changed.

5/2010 Revised Label

Patients should be advised that MS CONTIN[®] is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

7/2012 Revised Label – Section 17

Inform patients that MS CONTIN contains morphine, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share MS CONTIN with others and to take steps to protect MS CONTIN from theft or misuse.

V. April 16, 2014

1. The **Black Box Warning** in the **Highlights of Prescribing Information** had a change in language.

7/2012 Revised Label – Black Box Warning
MS CONTIN contains morphine sulfate, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during MS CONTIN therapy (5.1, 9).
4/2014 Revised Label – Black Box Warning
MS CONTIN exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors and conditions. (5.1)

2. The indication in **Section 1 Indications and Usage** was changed.

7/2012 Revised Label – Section 1
MS CONTIN is an opioid agonist product indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)
4/2014 Revised Label – Section 1
MS CONTIN is an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

3. The limitations of use in **Section 1 Indications and Usage** was changed to include language on abuse.

4/2014 Revised Label – Section 1 language added
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve MS CONTIN for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)

4. The **Boxed Warning** in the **Full Prescribing Information** was changed.

7/2012 Revised Label – Boxed Warning
MS CONTIN [®] contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit [see <i>Warnings and Precautions</i> (5.1)]. Assess each patient's risk for opioid abuse or addiction prior to prescribing MS CONTIN. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving MS CONTIN for signs of misuse, abuse, and addiction during treatment [see <i>Drug Abuse and Dependence</i> (9)].
4/2014 Revised Label – Boxed Warning
MS CONTIN [®] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing MS CONTIN, and monitor all patients regularly for the development of these behaviors or conditions [see <i>Warnings and Precautions</i> (5.1)].

5. The below language was added to **Section 2.1 Initial Dosing**

4/2014 Revised Label – Section 2.1
MS CONTIN should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.
MS CONTIN tablets must be taken whole. Crushing, chewing, or dissolving MS CONTIN tablets will result in uncontrolled delivery of morphine and can lead to overdose or death [see <i>Warnings and Precautions</i> (5.1)].

6. The language in **Section 2.2 Titration and Maintenance of Therapy** was changed.

7/2012 Revised Label – Section 2.2
Individually titrate MS CONTIN to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving MS CONTIN to assess the maintenance of pain control and the relative incidence of adverse reactions. During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), periodically reassess the continued need for the use of opioid analgesics.
If the level of pain increases, attempt to identify the source of increased pain, while adjusting the MS CONTIN dose to decrease the level of pain. Because steady-state plasma concentrations are approximated in 1 day, MS CONTIN dosage adjustments may be done every 1 to 2 days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid and non-opioid medication.
If signs of excessive opioid-related adverse reactions are observed, the next dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.
During chronic, around-the-clock opioid therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

4/2014 Revised Label – Section 2.2

Individually titrate MS CONTIN to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving MS CONTIN to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dose increase of MS CONTIN, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the MS CONTIN dose. Because steady-state plasma concentrations are approximated in 1 day, MS CONTIN dosage adjustments may be done every 1 to 2 days.

If unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

7. The language in **Section 2.4 Administration of MS CONTIN** was changed.

7/2012 Revised Label – Section 2.4

Instruct patients to swallow MS CONTIN tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of morphine *[see Warnings and Precautions (5.2)]*.

4/2014 Revised Label – Section 2.4

MS CONTIN tablets must be taken whole. Crushing, chewing, or dissolving MS CONTIN tablets will result in uncontrolled delivery of morphine and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

8. The below language was added to **Section 5.1 Addiction, Abuse, and Misuse**.

4/2014 Revised Label – Section 5.1 language added

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed MS CONTIN and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Abuse or misuse of MS CONTIN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of morphine and can result in overdose and death *[see Overdosage (10)]*.

9. The following sentence was removed from **Section 5.1 Addiction, Abuse, and Misuse**, “[r]outinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk of addiction even under appropriate medical use.”
10. Addiction, Abuse and Misuse were added to **Section 6 Adverse Reactions**.
11. In **Section 17 Patient Counseling Information** the first sentence was changed from “[i]nform patients that MS CONTIN contains morphine, a Schedule II controlled substance that is subject to abuse,” to

“[i]nform patients that the use of MS CONTIN, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death.”

VI. December 16, 2016

1. The below language was added to **Section 2.1 Dosage and Administration** and in the **Highlights of Prescribing Information**.

12/2016 Revised Label

To be prescribed only by healthcare providers knowledgeable in the use of potent opioids for management of chronic pain. (2.1)

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).

Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)

2. **Section 2.3 Discontinuation of MS CONTIN** had a change in language.

4/2014 Revised Label – Section 2.3

When the patient no longer requires therapy with MS CONTIN tablets, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue MS CONTIN.

12/2016 Revised Label – Section 2.3

When a patient no longer requires therapy with MS CONTIN tablets, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue MS CONTIN [see *Warnings and Precautions (5.12), Drug Abuse and Dependence (9.3)*].

3. **Section 2.4 Administration of MS CONTIN** was removed.

4/2014 Revised Label – Section 2.4 language removed

MS CONTIN tablets must be taken whole. Crushing, chewing, or dissolving MS CONTIN tablets will result in uncontrolled delivery of morphine and can lead to overdose or death [see *Warnings and Precautions (5.1)*].

4. Withdrawal was added to **Section 6 Adverse Reactions**.
5. The language from **9.1 Controlled Substance** was moved to **Section 9.2 Abuse**. The new language says, “MS CONTIN contains morphine, a Schedule II controlled substance.”

6. In **Section 9.2 Abuse** the sentence “[d]rug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get ‘high’, or the use of steroids for performance enhancement and muscle build up.”

PURDUE
LABEL CHANGES FOR OXYCONTIN
(NDA 20553 & 22272)³

SUMMARY OF LABEL CHANGES

The FDA approved OxyContin on December 12, 1995. On April 5, 2010, the FDA approved a reformulation of OxyContin for tablets that featured tamper-resistant properties. A summary of label changes with regards to indications, abuse, addiction, and withdrawal is also provided below, as well as a more in-depth review of the label changes.⁴

Following is a summary of major label changes regarding indications, abuse, addiction, and withdrawal for NDA 20553/22272:

- **1997 to 2001 Physicians' Desk Reference**
 - a) The indication was changed in **Indications and Usage** to "OxyContin tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days."
 - b) The language on abuse was changed in the **Information for Patients/Caregivers** section.
 - c) The language in **Drug Abuse and Dependence** was substantially changed.
 - d) The language on **Physical Dependence and Withdrawal** was changed.
 - e) A new **Safety and Handling** section was added, "OxyContin...are solid dosage forms that pose no known health risk to health-care providers beyond that of any controlled substance. As with all such drugs, care should be taken to prevent diversion or abuse by proper handling."
- **2002 Physicians' Desk Reference**
 - a) A **Black Box Warning** was added with language on abuse.
 - b) The indication changed in **Indications and Usage** to "OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride

³ Source: Label Information, NDA 022272, available at <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=022272>; 1995 Draft Package Insert, PURCHI-000621046; OxyContin (1997). In *Physicians' Desk Reference* (51st ed., pp. 2163-2167) Montvale, NJ: PDR Network; OxyContin (1998). In *Physicians' Desk Reference* (52nd ed., pp. 2344-2348) Montvale, NJ: PDR Network; OxyContin (1999). In *Physicians' Desk Reference* (53rd ed., pp. 2569-2574) Montvale, NJ: PDR Network; OxyContin (2000). In *Physicians' Desk Reference* (54th ed., pp. 2537-2541) Montvale, NJ: PDR Network; OxyContin (2001). In *Physicians' Desk Reference* (55th ed., pp. 2697-2701) Montvale, NJ: PDR Network; OxyContin (2002). In *Physicians' Desk Reference* (56th ed., pp. 2912-2916) Montvale, NJ: PDR Network; OxyContin (2010). In *Physicians' Desk Reference* (64th ed., pp. 2807-2813) Montvale, NJ: PDR Network.

⁴ All labels were not available for review. The 1995 Draft Package Insert, labels from the Physicians' Desk Reference from 1997-2002 and 2010 were reviewed as well as all labels available through the FDA.

indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.”

- c) Limitations on use were added to **Indications and Usage**.
- d) A new section on **Misuse, Abuse and Diversion of Opioids** was added under **Warnings**.
- e) The section on **Drug Abuse and Addiction** had a substantial change in language.
- f) **Cessation of Therapy** had a change in language.
- g) The section on **Safety and Handling** was substantially revised.

- **April 5, 2010**

- a) The **Boxed Warning** in **Full Prescribing Information** was changed to include language on persons at increased risk of opioid abuse.
- b) Language on abuse was added to **Section 2.2 Initiating Therapy with OxyContin**.
- c) **Misuse, Abuse and Diversion of Opioids** was removed from **Section 5 Warnings**.
- d) Drug abuse, addiction, and dependence were added to **Section 6 Adverse Reactions**.
- e) **Section 9.2 Abuse** underwent substantial revisions.

- **July 9, 2012**

- a) The **Boxed Warning** in the **Highlights of Prescribing Information** was changed to: “OxyContin contains oxycodone, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during OxyContin therapy.”
- b) The **Boxed Warning** in the **Full Prescribing Information** section was changed.
- c) Language on abuse was added to **Section 2.1 Initial Dosing**.
- d) A new **Section 2.2 Titration and Maintenance of Therapy** was added.
- e) A new **Section 5.1 Abuse Potential** was added.
- f) A new **Section 5.12 Avoidance of Withdrawal** was added.
- g) The language in **Section 9.2 Abuse** was substantially revised.
- h) **Section 9.3 Dependence** was changed.
- i) The language on abuse in **Section 17 Patient Counseling Information** was changed to: “Inform patients that OxyContin contains oxycodone, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share OxyContin with others and to take steps to protect OxyContin from theft or misuse.”

- **April 16, 2013**

- a) **Section 9.2 Abuse** was changed to add information on *Abuse Deterrence Studies*.

- **April 16, 2014**

- a) The **Black Box Warning** in the **Highlights of Prescribing Information** was changed to: “OXYCONTIN exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess each patient’s

risk before prescribing and monitor regularly for development of these behaviors and conditions.”

- b) The indication in **Section 1 Indications and Usage** was changed to:
“OXYCONTIN is an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which treatment options are inadequate.”
- c) The limitations of use in **Section 1 Indications and Usage** added language on abuse.
- d) The **Black Box Warning** in **Full Prescribing Information** was changed.
- e) **Section 5.1 Addiction, Abuse, and Misuse** had a change in language.
- **August 25, 2015**
 - a) The indication was changed in **Section 1 Indications and Usage** to include language on prescribing for pediatric patients.
 - b) A new **Section 2.1 Important Dosing and Administration Instructions** was added.
- **December 16, 2016**
 - a) **Section 2.9 Discontinuation of OxyContin** had a change in language.
 - b) Withdrawal was added to **Section 6 Adverse Reactions**.

DETAILED REVIEW OF LABEL CHANGES

I. 1997 to 2001 Physicians' Desk Reference ("PDR") Labels

1. The indication changed in **Indications and Usage**.

1995 Package Insert
OxyContin is a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of pain. (See: CLINICAL PHARMACOLOGY; CLINICAL TRIALS).
1997-2001 PDR
OxyContin™ tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days. (See: CLINICAL PHARMACOLOGY; CLINICAL TRIALS).

2. The language on abuse was changed in the **Information for Patients/Caregivers** section.

1995 Package Insert
While the appropriate medical use of oxycodone is unlikely to cause psychological dependence ("addiction"), oxycodone is one of a class of drugs known to be subject to abuse.
1997-2001 PDR
Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

3. The language in **Drug Abuse and Dependence** was substantially changed.

1995 Package Insert
Psychological dependence (addiction) to opioids is characterized by an overwhelming preoccupation with the procurement, hoarding, and abuse of these drugs for non-medicinal purposes. Psychological dependence is best treated utilizing a multi-disciplinary approach, but recidivism is common. Iatrogenic "addiction" is very rare and tolerance as well as physical dependence are not signs of psychological dependence; nor is psychological dependence necessarily accompanied by tolerance and physical dependence.

Abuse of opioids can occur in the absence of true psychological dependence and is characterized by occasional misuse for non-medical purposes.

OxyContin consists of a dual-polymer matrix, which prevents easy preparation of the tablet for parenteral abuse. Parenteral venous injection of a suspension of tablet constituents, which includes oxycodone, can result in local tissue necrosis and may be associated with talc contamination of the lungs.

Abuse Potential in Human Trials

In ex-addict prisoner volunteers, parenteral oxycodone was considered to have comparable abuse liability to parenteral morphine in doses that are equianalgesic to those studied in patients with pain. Whether or not the controlled-release oral dosage form would have the same abuse liability has not been studied.

Abuse Liability in Clinical Use

Iatrogenic addiction to opioids is very rare in the management of chronic pain. Psychological dependence (addiction) and substance abuse have been shown not to be major concerns when dealing with physically dependent or opioid-tolerant patients who suffer from chronic pain. In clinical trials involving 713 patients, addiction to **OxyContin** was not reported.

1997-2001 PDR

OxyContin™ is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone products are common targets for both drug abusers and drug addicts. Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.

Drug addiction (drug dependence, psychological dependence) is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug dependence is treatable, utilizing a multi-disciplinary approach, but relapse is common. Iatrogenic "addiction" to opioids legitimately used in the management of pain is very rare. "Drug seeking" behavior is very common to addicts. Tolerance and physical dependence in pain patients are *not* signs of psychological dependence. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Most chronic pain patients limit their intake of opioids to achieve a balance between the benefits of the drug and dose-limiting side effects. Physicians should be aware that psychological dependence may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true psychological dependence and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis and pulmonary granulomas.

4. The language on **Physical Dependence and Withdrawal** was changed.

1995 Package Insert

Opioid analgesics like many pharmaceuticals may cause physical dependence when used chronically. Such dependence, when it does occur, usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone or mixed agonist/antagonist analgesics (pentazocine, etc.; See also OVERDOSAGE). If OxyContin is abruptly discontinued, a moderate to severe abstinence syndrome may occur characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, gooseflesh, restless sleep or "yep" and mydriasis during the first 24 hours. These symptoms often increase in severity and over the next 72 hours may be accompanied by increasing irritability, anxiety, weakness, twitching and spasms of muscles, kicking movements, severe backache, abdominal and leg pains, abdominal and muscle cramps, hot and cold flashes, insomnia, nausea, anorexia, vomiting, intestinal spasm, diarrhea, coryza and repetitive sneezing, and increase in body temperature, blood pressure, respiratory rate and heart rate. Because of excessive loss of fluids through sweating, vomiting and diarrhea, there is usually marked weight loss, dehydration, ketosis, and disturbances in acid-base balance. Cardiovascular collapse can occur. Most observable symptoms disappear in 5 to 14 days. There appears to be a phase of secondary or chronic abstinence

which may last for 2 to 6 months characterized by insomnia, irritability, and muscular aches.

If signs and symptoms of withdrawal are present, patients should be treated by gradual, tapered dose reduction of OxyContin therapy and symptomatic support (see DOSAGE AND ADMINISTRATION: CESSATION OF THERAPY).

1997-2001 PDR

Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity (see OVERDOSAGE). If OxyContin is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. This is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate or heart rate. If signs and symptoms of withdrawal occur, patients should be treated by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of OxyContin combined with symptomatic support (see DOSAGE AND ADMINISTRATION: Cessation of Therapy).

5. A new **Safety and Handling** Section was added.

1997-2001 PDR

OxyContin® (oxycodone hydrochloride controlled-release) tablets are solid dosage forms that pose no known health risk to health-care providers beyond that of any controlled substance. As with all such drugs, care should be taken to prevent diversion or abuse by proper handling.

II. 2002 Physicians Desk Reference

1. A new **Black Box Warning** was added.

2002 PDR

WARNING:
OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. OxyContin Tablets are NOT intended for use as a prn analgesic. OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids. OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

2. The indication changed in **Indications and Usage**.

1997-2001 PDR
OxyContin® tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days (see CLINICAL PHARMACOLOGY; CLINICAL TRIALS).
2002 PDR
INDICATIONS AND USAGE OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

3. Limitations on use were added to **Indications and Usage**.

2002 PDR
OxyContin is NOT intended for use as a prn analgesic. Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society. OxyContin is not indicated for pain in the immediate postoperative period (the first 12–24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

4. A new section on **Misuse, Abuse and Diversion of Opioids** was added under **Warnings**.

2002 PDR
<p>Misuse, Abuse and Diversion of Opioids</p> <p>Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.</p> <p>Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.</p> <p>OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS and DRUG ABUSE AND ADDICTION).</p> <p>Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.</p> <p>Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.</p>

5. The section on **Withdrawal** added the sentence, “[p]hysical dependence and tolerance are unusual during chronic opioid therapy.” The sentence “[i]f signs and symptoms of withdrawal occur, patients should be treated by restitution of opioid therapy followed by a gradual, tapered dose reduction of OxyContin combined with symptomatic support” was changed to “[i]n general, opioids should not be abruptly discontinued.”

6. The section on **Drug Abuse and Addiction** had a substantial change in language.

1997-2001 PDR

OxyContin® is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone products are common targets for both drug abusers and drug addicts. Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.

Drug addiction (drug dependence, psychological dependence) is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug dependence is treatable, utilizing a multi-disciplinary approach, but relapse is common. Iatrogenic "addiction" to opioids legitimately used in the management of pain is very rare. "Drug seeking" behavior is very common to addicts. Tolerance and physical dependence in pain patients are not signs of psychological dependence. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Most chronic pain patients limit their intake of opioids to achieve a balance between the benefits of the drug and dose-limiting side effects.

Physicians should be aware that psychological dependence may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true psychological dependence and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis and pulmonary granulomas.

2002 PDR

OxyContin® is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

7. The section on **Cessation of Therapy** had a change in language.

1997-2001 PDR

When the patient no longer requires therapy with OxyContin tablets, patients receiving doses of 20–60 mg/day can usually have the therapy stopped abruptly without incident. However, higher doses should be tapered over several days to prevent signs and symptoms of withdrawal in the physically dependent patient. The daily dose should be reduced by approximately 50% for the first two days and then reduced by 25% every two days thereafter until the total dose reaches the dose recommended for opioid naive patients (10 or 20 mg q12h). Therapy can then be discontinued.

If signs of withdrawal appear, tapering should be stopped. The dose should be slightly increased until the signs and symptoms of opioid withdrawal disappear. Tapering should then begin again but with longer periods of time between each dose reduction.

2002 PDR

Cessation of Therapy

When the patient no longer requires therapy with OxyContin Tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

8. The section on **Safety and Handling** was substantially changed.

1997-2001 PDR

OxyContin® (oxycodone hydrochloride controlled-release) tablets are solid dosage forms that pose no known health risk to health-care providers beyond that of any controlled substance. As with all such drugs, care should be taken to prevent diversion or abuse by proper handling.

2002 PDR

OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

III. **2010 Physicians' Desk Reference**

1. The following sentence was removed from the **Misuse, Abuse and Diversion of Opioids** section: "[t]he development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare."
2. The following sentence was added to the **Drug Abuse and Addiction** section: "[t]here is a potential for drug addiction to develop following exposure to opioids, including oxycodone."

IV. **April 5, 2010**

1. The below language was added to the **Boxed Warning** in the **Full Prescribing Information** section.

4/2010 Original Label (new formulation) – Boxed Warning

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. (2.2)

2. The below language in the **Boxed Warning, Section 2 Dosage and Administration, and Section 5.1 Information Essential for Safe Administration** on altering tablets was slightly changed.

2010 PDR – Boxed Warning

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

4/2010 Original Label – Boxed Warning

OxyContin must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone. (2.1)

3. Language on abuse was added to **Section 2.2 Initiating Therapy with OxyContin**.

4/2010 Original Label – Section 2.2

risk factors for abuse or addiction; including whether the patient has a previous or current substance abuse problem, a family history of substance abuse, or a history of mental illness or depression;

4. The section on **Misuse, Abuse and Diversion of Opioids** was removed from **Section 5 Warnings**.
5. Drug abuse, addiction and dependence were added to **Section 6 Adverse Reactions**.
6. **Section 9.2 Abuse** had substantial changes in language.

2010 PDR

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. There is a potential for drug addiction to develop following exposure to opioids, including oxycodone. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical pur-

poses, often in combination with other psychoactive substances. OxyContin, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

4/2010 Original Label – Section 9.2

Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances.

With parenteral abuse, the tablet excipients can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Opioid drugs are sought by people with substance use disorders (abuse or addiction, the latter of which is also called “substance dependence”) and criminals who supply them by diverting medicines out of legitimate distribution channels. OxyContin is a target for theft and diversion.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, altering or forging of prescriptions and reluctance to provide prior

medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among people with untreated substance use disorders, and criminals who divert controlled substances.

The risks of misuse and abuse should be considered when prescribing or dispensing OxyContin. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.

Compromising an extended or controlled-release delivery system will result in the uncontrolled delivery of oxycodone and pose a significant risk to the abuser that could result in overdose and death [see *Warnings and Precautions (5.1)*]. The risk of fatal overdose is further increased when oxycodone is abused concurrently with alcohol or other CNS depressants, including other opioids [see *Warnings and Precautions (5.3)*]. Abuse may occur by taking intact tablets without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation.

Drug addiction is characterized by compulsive abuse, repeated use for non-medical purposes, loss of control over intake, craving of psychic effects and continued abuse despite harm or risk of harm in medical, social, legal or occupational domains. There is a potential for drug addiction to develop following exposure to opioids, including oxycodone. Drug addiction is a treatable disease, but relapse is common.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by intentional misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin has been diverted for non-medical use.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, proper dispensing and correct storage and handling are appropriate measures that help to limit misuse and abuse of opioid drugs. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

V. **July 9, 2012**

1. The **Boxed Warning** in the **Highlights of Prescribing Information** section was changed.

4/2010 Original Label – Boxed Warning
OxyContin contains oxycodone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (9)
7/2012 Revised Label – Boxed Warning
OxyContin contains oxycodone, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during OxyContin therapy (5.1, 9).

2. The **Boxed Warning** in the **Full Prescribing Information** section was changed.

4/2010 Original Label – Boxed Warning
OxyContin contains oxycodone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (9)
OxyContin can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9.2)
Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. (2.2)
7/2012 Revised Label – Boxed Warning
OxyContin[®] contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit [see Warnings and Precautions (5.1)]. Assess each patient’s risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving OxyContin for signs of misuse, abuse, and addiction during treatment [see Drug Abuse and Dependence (9)].

3. The below language on abuse was removed from **Section 2.1 Initial Dosing**.

4/2010 Original Label – Section 2.1 language removed
risk factors for abuse or addiction; including whether the patient has a previous or current substance abuse problem, a family history of substance abuse, or a history of mental illness or depression;

4. A new **Section 2.2 Titration and Maintenance of Therapy** was added.

7/2012 Revised Label – Section 2.2 language added

Individually titrate OxyContin to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OxyContin to assess the maintenance of pain control and the relative incidence of adverse reactions. During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), periodically reassess the continued need for the use of opioid analgesics.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the OxyContin dose to decrease the level of pain. Because steady-state plasma concentrations are approximated in 1 day, OxyContin dosage adjustments may be done every 1 to 2 days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid and non-opioid medication.

If signs of excessive opioid-related adverse reactions are observed, the next dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose, each time an increase is clinically indicated.

During chronic, around-the-clock opioid therapy, especially for non-cancer pain syndromes, reassess the continued need for around-the-clock opioid therapy regularly (e.g., every 6 to 12 months) as appropriate.

5. “Do not abruptly discontinue OxyContin” was added to **Section 2.4 Discontinuation of OxyContin**.

6. A new **Section 5.1 Abuse Potential** was added.

7/2012 Revised Label – Section 5.1 language added

OxyContin contains oxycodone, an opioid agonist and a Schedule II controlled substance. Oxycodone can be abused in a manner similar to other opioid agonists legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OxyContin in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient’s risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of OxyContin by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death [see *Overdosage (10)*].

Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

7. A new **Section 5.12 Avoidance of Withdrawal** was added.

7/2012 Revised Label – Section 5.12 language added
<p>Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including OxyContin. In these patients, mixed agonists/antagonists analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.</p> <p>When discontinuing OxyContin, gradually taper the dose [<i>see Dosage and Administration (2.4)</i>]. Do not abruptly discontinue OxyContin.</p>

8. The language in **Section 9.1 Controlled Substance** was changed.

4/2010 Original Label – Section 9.1
<p>OxyContin contains oxycodone, which is a Schedule II controlled substance with an abuse liability similar to morphine. OxyContin, like morphine and other opioids used for analgesia, can be abused and is subject to criminal diversion.</p>
7/2012 Revised Label – Section 9.1
<p>OxyContin contains oxycodone, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. OxyContin can be abused and is subject to misuse, addiction, and criminal diversion [<i>see Warnings and Precautions (5.1)</i>].</p> <p>The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.</p>

9. The language in **Section 9.2** was substantially revised.

4/2010 Original Label – Section 9.2
<p>Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances.</p> <p>With parenteral abuse, the tablet excipients can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.</p> <p>Opioid drugs are sought by people with substance use disorders (abuse or addiction, the latter of which is also called “substance dependence”) and criminals who supply them by diverting medicines out of legitimate distribution channels. OxyContin is a target for theft and diversion.</p> <p>“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, altering or forging of prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among people with untreated substance use disorders, and criminals who divert controlled substances.</p>

The risks of misuse and abuse should be considered when prescribing or dispensing OxyContin. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.

Compromising an extended or controlled-release delivery system will result in the uncontrolled delivery of oxycodone and pose a significant risk to the abuser that could result in overdose and death [see *Warnings and Precautions* (5.1)]. The risk of fatal overdose is further increased when oxycodone is abused concurrently with alcohol or other CNS depressants, including other opioids [see *Warnings and Precautions* (5.3)]. Abuse may occur by taking intact tablets without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation.

Drug addiction is characterized by compulsive abuse, repeated use for non-medical purposes, loss of control over intake, craving of psychic effects and continued abuse despite harm or risk of harm in medical, social, legal or occupational domains. There is a potential for drug addiction to develop following exposure to opioids, including oxycodone. Drug addiction is a treatable disease, but relapse is common.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by intentional misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin has been diverted for non-medical use.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, proper dispensing and correct storage and handling are appropriate measures that help to limit misuse and abuse of opioid drugs. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

7/2012 Revised Label – Section 9.2

Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug seeking" behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

OxyContin, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests as required by state law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to reduce abuse of opioid drugs.

Risks Specific to Abuse of OxyContin

OxyContin is for oral use only. Abuse of OxyContin poses a risk of overdose and death. This risk is increased with concurrent abuse of OxyContin with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved OxyContin enhances drug release and increases the risk of over dose and death.

Abuse may occur by taking intact tablets without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation.

With parenteral abuse, the tablet excipients can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

10. Section 9.3 Dependence was substantially revised.

4/2010 Original Label – Section 9.3

Physical dependence to an opioid is manifested by characteristic withdrawal signs and symptoms after abrupt discontinuation of a drug, significant dose reduction or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome in adults is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. [See *Use In Specific Populations* (8.2)]

In general, opioids should not be abruptly discontinued [see *Dosage and Administration* (2.9)].

7/2012 Revised Label – Section 9.3

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OxyContin should not be abruptly discontinued [*see Dosage and Administration (2.4)*]. If OxyContin is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see Use in Specific Populations (8.9)*].

11. The language on abuse was changed in **Section 17 Patient Counseling Information.**

4/2010 Original Label – Section 17

Advise patients that OxyContin is a drug with known abuse potential. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

7/2012 Revised Label – Section 17

Abuse Potential

Inform patients that OxyContin contains oxycodone, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share OxyContin with others and to take steps to protect OxyContin from theft or misuse.

VI. **April 16, 2013**

1. **Section 9.2 Abuse** was revised to include the below information on Abuse Deterrence Studies.

1/2013 Revised Label – Section 9.2 language added

OxyContin is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OxyContin resulting from a change in formulation, in this

section, the original formulation of OxyContin, which is no longer marketed, will be referred to as “original OxyContin” and the reformulated, currently marketed product will be referred to as OxyContin.

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OxyContin to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OxyContin relative to an immediate-release oxycodone. When subjected to an aqueous environment, OxyContin gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies

In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OxyContin 30 mg tablets, coarsely crushed OxyContin 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OxyContin, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug-liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response (‘definitely would not take drug again’) and 100 represents the strongest positive response (‘definitely would to take drug again’).

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects’ nostrils occurred in 34% (n=10) of subjects with finely crushed OxyContin, compared with 7% (n=2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OxyContin was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 2.

Table 2. Summary of Maximum Drug Liking (E_{max}) Data Following Intranasal Administration

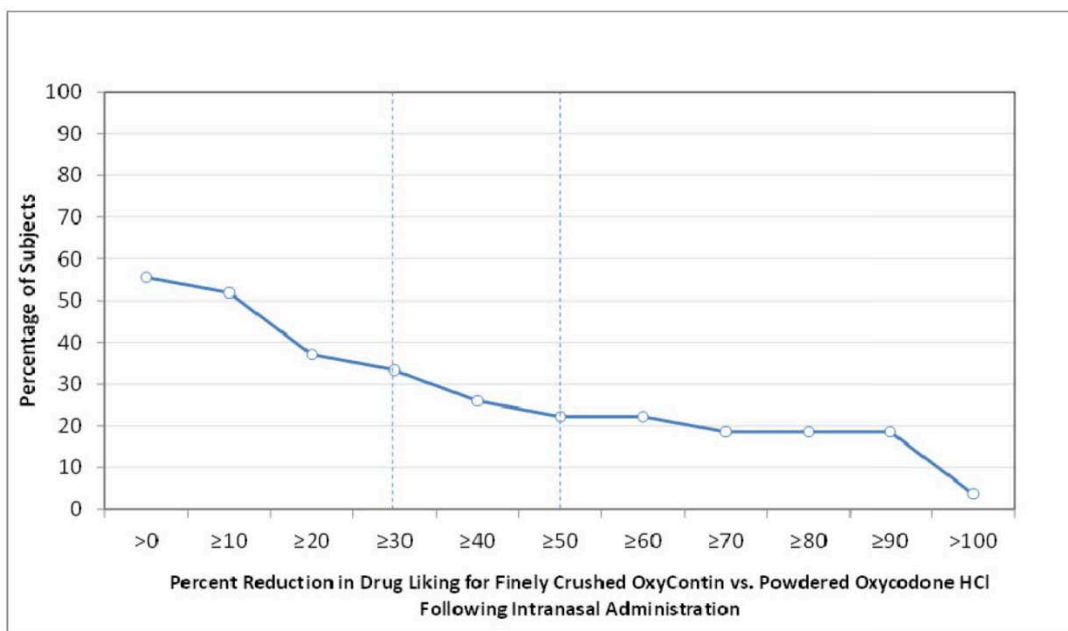
VAS Scale (100 mm)*		OxyContin (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)

	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed OxyContin compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OxyContin vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OxyContin relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OxyContin relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with OxyContin compared to oxycodone HCl, and approximately 22% (n = 6) of subjects had a reduction of at least 50% in drug liking with OxyContin compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for OxyContin vs. oxycodone HCl, N=27 Following Intranasal Administration



The results of a similar analysis of drug liking for finely crushed OxyContin relative to finely crushed original OxyContin were comparable to the results of finely crushed OxyContin relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no reduction in liking with OxyContin relative to original OxyContin. Approximately 57% (n = 16) of subjects

had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n= 8) of subjects had a reduction of at least 50% in drug liking with OxyContin compared to original OxyContin.

Summary

The *in vitro* data demonstrate that OxyContin has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that OxyContin has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OxyContin by these routes, as well as by the oral route is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OxyContin on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OxyContin contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OxyContin can be abused and is subject to misuse, addiction, and criminal diversion [See *Warnings and Precautions (5.1)* and *Drug Abuse and Dependence (9.1)*].

VII. **April 16, 2014**

1. The **Black Box Warning** in the **Highlights of Prescribing Information** was changed.

4/2013 Revised Label
OxyContin contains oxycodone, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during OxyContin therapy (5.1, 9).
4/2014 Revised Label
OXYCONTIN exposes users to risks of addictions, abuse and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors and conditions. (5.1)

2. The indication was changed in **Section 1 Indications and Usage** and the **Highlights of Prescribing Information**.

4/2013 Revised Label
OxyContin is an opioid agonist product indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

4/2014 Revised Label

OXYCONTIN is an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

3. The limitations of use in **Section 1 Indications and Usage** and the **Highlights of Prescribing Information** were changed to include language on abuse.

4/2014 Revised Label – Section 1 language added

Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release formulations, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)

4. The **Black Box Warning** in the **Full Prescribing Information** section was changed.

4/2013 Revised Label – Black Box Warning

OxyContin[®] contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit [see *Warnings and Precautions (5.1)*]. Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving OxyContin for signs of misuse, abuse, and addiction during treatment [see *Drug Abuse and Dependence (9)*].

4/2014 Revised Label – Black Box Warning

OXYCONTIN[®] exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OXYCONTIN and monitor all patients regularly for the development of these behaviors or conditions [see *Warnings and Precautions (5.1)*].

5. The below language was added to **Section 2.1 Initial Dosing**.

4/2014 Revised Label – Section 2.1 language added

OXYCONTIN should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

OXYCONTIN tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth [see *Patient Counseling Information (17)*]. Crushing, chewing, or dissolving OXYCONTIN tablets will result in uncontrolled delivery of oxycodone and can lead to overdose or death [see *Warnings and Precautions (5.1)*].

6. The underlined portion of the following sentence was added in **Section 2.2 Titration and Maintenance of Therapy**: “[c]ontinually reevaluate patients receiving OxyContin to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse and misuse.”
7. The below language was added to section **2.2 Titration and Maintenance of Therapy**.

4/2014 Revised Label – Section 2.2 language added

Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

Patients who experience breakthrough pain may require a dose increase of OXYCONTIN or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level

8. **Section 5.1 Addiction, Abuse, and Misuse** had a change in language.

4/2013 Revised Label – Section 5.1

OxyContin contains oxycodone, an opioid agonist and a Schedule II controlled substance. Oxycodone can be abused in a manner similar to other opioid agonists legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OxyContin in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient’s risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of OxyContin by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death [see *Drug Abuse and Dependence (9)* and *Overdosage (10)*].

Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

4/2014 Revised Label – Section 5.1

OXYCONTIN contains oxycodone, a Schedule II controlled substance. As an opioid, OXYCONTIN exposes users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*]. As modified-release products such as OXYCONTIN deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present [*see Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OXYCONTIN. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse or misuse prior to prescribing OXYCONTIN, and monitor all patients receiving OXYCONTIN for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as OXYCONTIN, but use in such patients necessitates intensive counseling about the risks and proper use of OXYCONTIN along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse, or misuse of OXYCONTIN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and death [*see Overdosage (10)*].

Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OXYCONTIN. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

9. "Drug abuse, addiction, and dependence" in **Section 6 Adverse Reactions** was changed to "Addiction, Abuse, and Misuse."
10. "Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances" was removed from **Section 9.2 Abuse**.
11. The language in **Section 17 Patient Counseling Information** was changed.

4/2013 Revised Label – Section 17

Inform patients that OxyContin contains oxycodone, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share OxyContin with others and to take steps to protect OxyContin from theft or misuse.

4/2014 Revised Label – Section 17

Inform patients that the use of OXYCONTIN, even when taken as recommended can result in addiction, abuse and misuse, which can lead to overdose and death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share OXYCONTIN with others and to take steps to protect OXYCONTIN from theft or misuse.

VIII. August 13, 2015

1. The indication was changed in **Section 1 Indications and Usage**.

4/2014 Revised Label – Section 1

OXYCONTIN is an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

8/2015 Revised Label – Section 1

OXYCONTIN is an opioid agonist indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

2. The below language was added to **Dosage and Administration** in the **Highlights of Prescribing Information**.

8/2015 Revised Label language added

To be prescribed only by health care providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)

3. A new **Section 2.1 Important Dosage and Administration Instructions** was added.

8/2015 Revised Label – Section 2.1 language added

OXYCONTIN should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

- Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.1)*].

IX. **December 16, 2016**

1. The below language was added to **Section 2.1 Important Dosage and Administration Instructions** and the **Highlights of Prescribing Information**.

12/2016 Revised Label – Section 2.1 language added

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).

Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)

2. **Section 2.9 Discontinuation of OXYCONTIN** had a change in language.

8/2015 Revised Label – Section 2.9

When the patient no longer requires therapy with OXYCONTIN, gradually titrate the dosage downward to prevent signs and symptoms of withdrawal in the physically dependent patient. Do not abruptly discontinue OXYCONTIN.

12/2016 Revised Label – Section 2.9

When the patient no longer requires therapy with OXYCONTIN, taper the dosage gradually, by 25% to 50% every 2 to 4 days, while monitoring for signs and symptoms of withdrawal. If a patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OXYCONTIN *[see Warnings and Precautions (5.13), Drug Abuse and Dependence (9.3)]*.

3. Withdrawal was added to **Section 6 Adverse Reactions**.
4. **Section 9.1 Controlled Substance** was changed to “OXYCONTIN contains oxycodone, a Schedule II controlled substance.” The remaining language was moved to **Section 9.2 Abuse**.
5. “Drug abuse includes, but is not limited to, the following examples: the use of a prescription or over-the-counter drug to get ‘high’, or the use of steroids for performance enhancement and muscle build up” was removed from **Section 9.2 Abuse**.

PURDUE
LABEL CHANGES FOR BUTRANS
(NDA 21306)⁵

The FDA approved Butrans on June 30, 2010. A summary of label changes with regards to indications, abuse, addiction, and withdrawal is provided below, as well as a more in-depth review of the label changes.

Following is a summary of major label changes regarding indications, abuse, addiction, and withdrawal for NDA 22306:

- **July 1, 2011**
 - a) There were no changes from the original June 30, 2010 label.
- **July 9, 2012**
 - a) The language regarding abuse was changed in the **Boxed Warning** in the **Highlights of Prescribing Information** was changed to add the sentence, “[m]onitor for signs of misuse, abuse, and addiction during BUTRANS therapy.” “Access patients for their clinical risks for opioid abuse or addiction prior to prescribing opioids” was removed.
 - b) Limitations on Use were added to **Section 1 Indications and Usage**.
 - c) **Section 5.1 Abuse Potential** had a change in language with the substance
 - i. “Data are not available to establish the true incidence of addiction in patients with chronic pain treated with opioids” was removed.
 - ii. “Misuse or abuse of BUTRANS by chewing, swallowing, snorting or injecting buprenorphine extracted from the transdermal system will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death” was added.
 - d) A new **Section 5.17 Avoidance of Withdrawal** was added.
 - e) **Section 9.2 Abuse** had a substantial change in language with the below language added.
 - i. “All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effect. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get ‘high’, or the use of steroids for performance enhancement and muscle build up.”
 - ii. “Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful

⁵ Source: Label Information, NDA 201306, available at <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=021306>.

consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.”

- iii. “Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.”
- iv. “BUTRANS may be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state law, is strongly advised.”

- **April 16, 2014**

- a) The **Boxed Warning** language for abuse in the **Highlights of Prescribing Information** was changed to, “BUTRANS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk before prescribing, and monitor for development of these behaviors or conditions.”
- b) The indication in **Section 1 Indications and Usage** was changed to: “BUTRANS is a partial opioid agonist product identified for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.”
- c) The limitations of use in **Section 1 Indications and Usage** was changed to include language on abuse: “Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve BUTRANS for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.”
- d) The **Boxed Warning** in the **Full Prescribing Information** was changed to: “BUTRANS exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk prior to prescribing BUTRANS, and monitor all patients regularly for the development of these behaviors or conditions.”
- e) Additional language was added to **Section 5.1 Addiction, Abuse, and Misuse**
- f) Addiction, Abuse, and Misuses was added to **Section 6 Adverse Reactions**
- g) Language was removed from **Section 9.2 Abuse**
- h) The language on abuse was changed in **Section 17 Patient Counseling Information** to: “Inform patients that the use of BUTRANS, even when taken as recommended, can result in addiction, abuse, and misuse, which could lead to overdose and death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share BUTRANS with others and to take steps to protect BUTRANS from theft or misuse.

- **June 30, 2014**
 - a) There were no changes from the April 16, 2014 label.
- **December 16, 2016**
 - a) The **Dosage and Administration** in the **Highlights of Prescribing Information** added the following information:
 - i. “To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain.”
 - ii. “Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.”
 - iii. Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse.”
 - b) **Section 2.1 Dosage and Administration** added the sentence: “[u]se the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.”
 - c) Additional language was added to **Section 9.2 Abuse**.
 - i. “The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.”
 - ii. “Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.”
- **October 13, 2017**
 - a) No changes from December 16, 2016 label.

DETAILED REVIEW OF LABEL CHANGES

I. July 9, 2012

1. The language in the **Boxed Warning** regarding addiction, abuse, and misuse was changed. The indication was also removed from this section in the revised label.

6/2010 Original Label – Boxed Warning

- **Butrans is indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. (1)**
- **Butrans contains buprenorphine which is a mu opioid partial agonist and a Schedule III controlled substance. (9.1)**
- **Assess patients for their clinical risks for opioid abuse or addiction prior to prescribing opioids. (2.2)**

7/2012 Revised Label – Boxed Warning

- **BUTRANS contains buprenorphine, a Schedule III controlled substance. Monitor for signs of misuse, abuse, and addiction during BUTRANS therapy (5.1, 9).**

2. Limitations of Use were added to the **Indications and Usage** section in the **Highlights of Prescribing Information** and in **Section 1**.

7/2012 Revised Label – Indications and Usage in Highlights of Prescribing Information & Section 1 new language added

Limitations of Use

- BUTRANS is not for use:
 - As an as-needed (prn) analgesic (1)
 - For pain that is mild or not expected to persist for an extended period of time (1)
 - For acute pain (1)
 - For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time (1)

3. The **Dosage and Administration** section in the **Highlights of Prescribing Information** had a change in language.

6/2010 Original Label – Dosage and Administration in the Highlights of Prescribing Information

- Each Butrans is intended to be worn for 7-days. (2.1)
- In opioid-naïve patients, the initial dose of Butrans should always be 5 mcg/hour. (2.2)
- For patients already receiving opioids, consult conversion instructions. (2.2)
- Do not increase the Butrans dose until the patient has been exposed continually to the previous dose for 72 hours. (2.3)
- After removal, wait a minimum of 3 weeks before applying to the same site (2.1)
- When Butrans is no longer required by the patient, taper the dose as part of a comprehensive treatment plan. (2.5)

7/2012 Revised Label – Dosage and Administration in the Highlights of Prescribing Information

- Individualize dosing based on patient’s prior analgesic treatment experience, and titrate as needed to provide adequate analgesia and minimize adverse reactions. (2.1, 2.2)
- Instruct patients to wear BUTRANS for 7 days and to wait a minimum of 3 weeks before applying to the same site. (2.1)
- Do not abruptly discontinue BUTRANS in a physically dependent patient. (2.3, 5.17)

4. The **Black Box Warning** section in the **Full Prescribing Information** had a change in language regarding abuse potential.

6/2010 Original Label – Black Box Warning section in the Full Prescribing Information

Potential for Abuse

Butrans contains buprenorphine which is a mu opioid partial agonist and a Schedule III controlled substance. Butrans can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the abuse potential when prescribing or dispensing Butrans in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9)

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Assess patients for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Routinely monitor all patients receiving opioids for signs of misuse, abuse and addiction. (2.2)

7/2012 Revised Label – Black Box Warning section in the Full Prescribing Information

Abuse Potential

BUTRANS contains buprenorphine, an opioid agonist and Schedule III controlled substance with an abuse liability similar to other Schedule III opioids, legal or illicit [see *Warnings and Precautions (5.1)*]. Assess each patient's risk for opioid abuse or addiction prior to prescribing BUTRANS. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving BUTRANS for signs of misuse, abuse, and addiction during treatment [see *Drug Abuse and Dependence (9)*].

5. **Section 2.3 Dose Titration** was moved to **Section 2.3 Titration and Maintenance of Therapy** and had a language change.

6/2010 Original Label – Section 2.2

Based on the patient's requirement for supplemental short-acting analgesics, upward titration may be instituted with a minimum Butrans titration interval of 72 hours, based on the pharmacokinetic profile and time to reach steady state levels [see *Clinical Pharmacology (12.3)*]. Individually titrate the dose, under close supervision, to a level that provides adequate analgesia with tolerable side effects.

The maximum Butrans dose is 20 mcg/hour. **Do not exceed a dose of one 20 mcg/hour Butrans system due to the risk of QTc interval prolongation.** In a clinical trial, Butrans 40 mcg/hour (given as two Butrans 20 mcg/hour systems) resulted in prolongation of the QTc interval [see *Warnings and Precautions (5.4)* and *Clinical Pharmacology (12.2)*].

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between the prescriber, other members of the healthcare team, the patient, and the caregiver/family. Advise patients and caregivers/family members of the potential side effects.

7/2012 Revised Label – Section 2.3

Individually titrate BUTRANS to a dose that provides adequate analgesia and minimizes adverse reactions. The minimum BUTRANS titration interval is 72 hours, based on the pharmacokinetic profile and time to reach steady state levels [see *Clinical Pharmacology (12.3)*].

The maximum BUTRANS dose is 20 mcg/hour. **Do not exceed a dose of one 20 mcg/hour BUTRANS system due to the risk of QTc interval prolongation.** In a clinical trial, BUTRANS 40 mcg/hour (given as two BUTRANS 20 mcg/hour systems) resulted in prolongation of the QTc interval [see *Warnings and Precautions (5.7)*, and *Clinical Pharmacology (12.2)*].

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the BUTRANS dose to decrease the level of pain. Because steady-state plasma concentrations are approximated within 72 hours, BUTRANS dosage adjustments may be done every 3 days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid or non-opioid medication.

If signs of excessive opioid-related adverse reactions are observed, the current patch may be removed or next dose may be reduced. Adjust the dose to obtain an appropriate balance between the management of pain and opioid-related adverse reactions.

6. **Section 2.4 Maintenance of Therapy and Supplemental Analgesia** was removed.

6/2010 Original Label – Section 2.3

2.4 Maintenance of Therapy and Supplemental Analgesia

The intent of the titration period is to establish a patient-specific weekly Butrans dose that will maintain adequate analgesia with tolerable side effects for as long as pain management is necessary. Immediate-release opioid and non-opioid medications can be used as supplemental analgesia during Butrans therapy.

During chronic opioid analgesic therapy with Butrans, reassess the continued need for around-the-clock opioid analgesic therapy periodically.

7. **Section 2.5 Cessation of Therapy** was moved to **Section 2.3 Cessation of Therapy** with a change in language.

6/2010 Original Label – Section 2.5

When the patient no longer requires therapy with Butrans, taper the dose gradually to prevent signs and symptoms of withdrawal in the physically-dependent patient; consider introduction of an appropriate immediate-release opioid medication. Undertake discontinuation of therapy as part of a comprehensive treatment plan.

7/2012 Revised Label – Section 2.3

2.3 Cessation of Therapy

When the patient no longer requires therapy with BUTRANS, use a gradual downward titration of the dose every 7 days to prevent signs and symptoms of withdrawal in the physically dependent patient; consider introduction of an appropriate immediate-release opioid medication. Do not abruptly discontinue BUTRANS.

8. **Section 5.7 Misuse, Abuse, and Diversion of Opioids** was moved to **Section 5.1 Abuse Potential** with a change in language

6/2010 Original Label – Section 5.7

Butrans contains buprenorphine, a partial agonist at the mu opioid receptor and a Schedule III controlled substance. Opioid agonists have potential for being abused, are sought by drug abusers and people with addiction disorders, and are subject to criminal diversion.

Butrans can be abused in a manner similar to other opioid agonists, legal or illicit. Consider this potential for abuse when prescribing or dispensing Butrans in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Monitor all patients receiving opioids for signs of abuse, misuse, and addiction. Furthermore, assess patients for their potential for opioid abuse prior to being prescribed opioid therapy. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse) or mental illness (e.g., depression). Opioids may still be appropriate for use in these patients; however, they will require intensive monitoring for signs of abuse.

Notwithstanding concerns about abuse, addiction, and diversion, provide proper management of pain. However, all patients treated with opioid agonists require careful monitoring for signs of abuse and addiction, since use of opioid agonist analgesic products carries the risk of addiction even under appropriate medical use [*see Drug Abuse and Dependence (9.2)*]. Data are not available to establish the true incidence of addiction in patients with chronic pain treated with opioids.

Abuse of Butrans poses a significant risk to the abuser that could potentially result in overdose or death [*see Drug Abuse and Dependence (9)*].

Contact your state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

7/2012 Revised Label – Section 5.1

BUTRANS contains buprenorphine, a partial agonist at the mu opioid receptor and a Schedule III controlled substance. Buprenorphine can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing BUTRANS in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient's risk for opioid abuse or addiction prior to prescribing BUTRANS. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of BUTRANS by chewing, swallowing, snorting or injecting buprenorphine extracted from the transdermal system will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death [see *Overdosage (10)*].

Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

9. A new **Section 5.17 Avoidance of Withdrawal** was added.

7/2012 Revised Label – Section 5.17

Symptoms of withdrawal include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Significant fluid losses from vomiting and diarrhea can require intravenous fluid administration.

When discontinuing BUTRANS, gradually taper the dose [see *Dosage and Administration (2.3)*]. Do not abruptly discontinue BUTRANS.

10. **Section 9.1 Controlled Substance** added the following language to the end of the first sentence, "...with an abuse potential similar to other Schedule III opioids."

11. The below language was removed from **Section 9.2 Abuse**.

6/2010 Original Language – Section 9.2 language removed

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Opioid drugs are sought by people with substance use disorders (abuse or addiction, the latter of which is also called "substance dependence") and criminals who supply them by diverting medicines out of legitimate distribution channels. Butrans is a target for theft and diversion.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, proper dispensing and correct storage and handling are appropriate measures that help to limit misuse and abuse of opioid drugs. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

12. The below language was added to **Section 9.2 Abuse**.

7/2012 Revised Label – Section 9.2 language added

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

BUTRANS may be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state law, is strongly advised.

13. In **Section 9.2 Abuse** the below sentences were changed.

6/2010 Original Label – Section 9.2

physician(s). “Doctor shopping” to obtain additional prescriptions is common among people with untreated substance use disorders, and criminals who divert controlled substances.

physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since Butrans may be diverted for non-medical use, careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

in overdose and death [see *Warnings and Precautions* (5.1)]. The risk of fatal overdose is further increased when buprenorphine is abused concurrently with alcohol or other CNS depressants, including other opioids and benzodiazepines [see *Warnings and Precautions* (5.3)]. Abuse may occur by applying

7/2012 Revised Label – Section 9.2

treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

BUTRANS is intended for transdermal use only. Abuse of BUTRANS poses a risk of overdose and death. This risk is increased with concurrent abuse of BUTRANS with alcohol and other substances including other opioids and benzodiazepines [see *Warnings and Precautions (5.6)*, and *Drug Interactions (7.2)*]. Compromising the transdermal delivery system will result in the uncontrolled

14. The below language was removed from **Section 9.3 Dependence**.

6/2010 Original Label – Section 9.3 language removed

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Tolerance could occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence to an opioid is manifested by characteristic withdrawal signs and symptoms after abrupt discontinuation of a drug, significant dose reduction, or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid analgesic therapy.

The opioid abstinence or withdrawal syndrome in adults is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate [see *Use In Specific Populations (8.2)*]

In general, opioids should not be abruptly discontinued [see *Dosage and Administration (2.9)*].

15. The below language was added to **Section 9.3 Dependence**.

7/2012 Revised Label – Section 9.3 language added

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, buprenorphine, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

BUTRANS should not be abruptly discontinued [see *Dosage and Administration (2.3)*]. If BUTRANS is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

16. The below language was removed from **Section 10 Overdosage**.

6/2010 Original Label – Section 10.1

Deaths due to overdose have been reported with abuse and misuse of buprenorphine. Review of case reports has indicated that the risk of fatal overdose is further increased when Butrans is abused concurrently with alcohol or other CNS depressants, including other opioids.

17. The language on abuse in **Section 17 Patient Counseling Information** was changed.

6/2010 Original Label – Section 17

Advise patients that buprenorphine is a drug that some people may abuse. They should use Butrans only as directed, and not give it to anyone other than the individual for whom it was prescribed. Protect it from theft. Be especially careful to keep this medication away from children and pets.

7/2012 Revised Label – Section 17

Inform patients that BUTRANS contains buprenorphine, a Schedule III controlled substance that is subject to abuse. Instruct patients not to share BUTRANS with others and to take steps to protect BUTRANS from theft or misuse.

II. April 16, 2014

1. The **Black Box Warning** in the **Highlights of Prescribing Information** was changed as to abuse.

7/2012 Revised Label – Black Box Warning in the Highlights of Prescribing Information

- **BUTRANS contains buprenorphine, a Schedule III controlled substance. Monitor for signs of misuse, abuse, and addiction during BUTRANS therapy (5.1, 9).**

4/2014 Revised Label – Black Box Warning in the Highlights of Prescribing Information

- **BUTRANS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patients risk before prescribing, and monitor for development of these behaviors or conditions. (5.1, 10)**

2. The indication in **Section 1 Indications and Usage** was changed.

7/2012 Revised Label – Section 1

BUTRANS is a partial opioid agonist product indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. (1)

4/2014 Revised Label – Section 1

BUTRANS is a partial opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. (1)

3. The limitations of use in **Section 1 Indications and Usage** were changed.

7/2012 Revised Label – Section 1
<p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • BUTRANS is not for use: <ul style="list-style-type: none"> – As an as-needed (prn) analgesic (1) – For pain that is mild or not expected to persist for an extended period of time (1) – For acute pain (1) – For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time (1)
4/2014 Revised Label – Section 1
<p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve BUTRANS for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1) • BUTRANS is not indicated as an as-needed (prn) analgesic. (1)

4. The **Boxed Warning** in the **Full Prescribing Information** was changed.

7/2012 Revised Label - Boxed Warning in the Full Prescribing Information
<p><u>Abuse Potential</u></p> <p>BUTRANS contains buprenorphine, an opioid agonist and Schedule III controlled substance with an abuse liability similar to other Schedule III opioids, legal or illicit <i>[see Warnings and Precautions (5.1)]</i>. Assess each patient's risk for opioid abuse or addiction prior to prescribing BUTRANS. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving BUTRANS for signs of misuse, abuse, and addiction during treatment <i>[see Drug Abuse and Dependence (9)]</i>.</p>
4/2014 Revised Label - Boxed Warning in the Full Prescribing Information
<p><u>Addiction, Abuse, and Misuse</u></p> <p>BUTRANS[®] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing BUTRANS, and monitor all patients regularly for the development of these behaviors or conditions <i>[see Warnings and Precautions (5.1) and Overdosage (10)]</i>.</p>

5. The below language was removed from **Section 2.1 Initial Dosing**.

7/2012 Revised Label – Section 2.1 language removed

Consider the following factors when selecting an initial dose of BUTRANS:

- Total daily dose, potency, and any prior opioid the patient has been taking previously;
- Reliability of the relative potency estimate used to calculate the equivalent dose of buprenorphine needed (Note: potency estimates may vary with the route of administration);
- Patient's degree of opioid experience and opioid tolerance;
- General condition and medical status of the patient;
- Concurrent medication;
- Type and severity of the patient's pain.

6. The below language was added to **Section 2.1 Initial Dosing**.

4/2014 Revised Label – Section 2.1 language added

BUTRANS should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

7. The below language was added to **Section 2.2 Titration and Maintenance of Therapy**.

4/2014 Revised Language – Section 2.2 language added

reactions. Continually reevaluate patients receiving BUTRANS to assess the maintenance of pain control and the relative incidence of adverse reactions, and monitor for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

achieved within 72 hours, BUTRANS dosage may be adjusted every 3 days. Dose adjustments may be made in 5 mcg/hour or 10 mcg/hour increments by using no more than two patches of the 5 mcg/hour or 10-mcg/hour system(s). The total dose from all patches should not exceed 20 mcg/hour. For the use of two patches, patients should be instructed to remove their current patch, and apply the two new patches adjacent to one another at a different application site [*see Dosage and Administration (2.5)*].

analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the BUTRANS dose.

If unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced.

8. The language on disposal from the earlier label in **Section 2.5 Administration of BUTRANS** was moved to **Section 2.6 Disposal Instructions** which a change in the language.

7/2012 Revised Label – Section 2.5

When changing the system, instruct patients to remove BUTRANS, fold it over on itself, and flush it down the toilet. Alternatively, BUTRANS can be sealed in the Patch-Disposal Unit provided and then disposed of in the trash. Never throw BUTRANS away in the trash without sealing it in the Patch-Disposal Unit.

4/2014 Revised Label – Section 2.6

Patients should refer to the Instructions for Use for proper disposal of BUTRANS. Dispose of used and unused patches by following the instructions on the Patch-Disposal Unit that is packaged with the BUTRANS patches.

Alternatively, patients can dispose of used patches by folding the adhesive side of the patch to itself, then flushing the patch down the toilet immediately upon removal. Unused patches should be removed from their pouches, the protective liners removed, the patches folded so that the adhesive side of the patch adheres to itself, and immediately flushed down the toilet.

Patients should dispose of any patches remaining from a prescription as soon as they are no longer needed.

9. The below new language was added to **Section 5.1 Addiction, Abuse, and Misuse.**

4/2014 Revised Label – Section 5.1 language added

As an opioid,

BUTRANS exposes users to the risks of addiction, abuse, and misuse. As modified-release products such as BUTRANS deliver the opioid over an extended period of time, there is a greater risk for overdose and death, due to the larger amount of buprenorphine present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed BUTRANS and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused [*see Drug Abuse and Dependence (9)*].

Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling Information (17)*].

10. In **Section 5.1 Section 5.1 Addiction, Abuse, and Misuse** the sentence, “[a]ccess each patient’s risk for opioid abuse or addiction prior to prescribing BUTRANS” was changed to “[a]ccess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing BUTRANS, and monitor all patients receiving BUTRANS for the development of these behaviors or conditions.”

11. The below language was changed in **Section 5.1 Addiction, Abuse, and Misuse.**

7/2012 Revised Label – Section 5.1

depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of BUTRANS by chewing, swallowing, snorting or injecting buprenorphine extracted from the transdermal system will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death *[see Overdosage (10)]*.

4/2014 Revised Label – Section 5.1

abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as BUTRANS, but use in such patients necessitates intensive counseling about the risks and proper use of BUTRANS, along with intensive monitoring for signs of addiction, abuse, or misuse.

Abuse or misuse of BUTRANS by placing it in the mouth, chewing it, swallowing it, or using it in ways other than indicated may cause choking, overdose and death *[see Overdosage (10)]*.

12. **Section 5.17 Avoidance of Withdrawal** was removed.

7/2012 Revised Label – Section 5.17 language removed

Symptoms of withdrawal include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Significant fluid losses from vomiting and diarrhea can require intravenous fluid administration.

When discontinuing BUTRANS, gradually taper the dose *[see Dosage and Administration (2.3)]*. Do not abruptly discontinue BUTRANS.

13. Addiction, Abuse, and Misuse was added to **Section 6 Adverse Reactions**.

14. The below language was removed from **Section 9.2 Abuse**.

7/2012 Revised Label – Section 9.2

Abuse of BUTRANS poses a hazard of overdose and death. This risk is increased with compromise of the BUTRANS Transdermal System and with concurrent abuse of alcohol or other substances. BUTRANS has been diverted for non-medical use.

The risks of misuse and abuse should be considered when prescribing or dispensing BUTRANS. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.

15. The below language was added to **Section 9.2 Abuse**.

4/2014 Revised Label – Section 9.2

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to reduce abuse of opioid drugs.

16. The language on abuse was changed in **Section 17 Patient Counseling Information**

7/2012 Revised Label – Section 17

Inform patients that BUTRANS contains buprenorphine, a Schedule III controlled substance that is subject to abuse. Instruct patients not to share BUTRANS with others and to take steps to protect BUTRANS from theft or misuse.

4/2014 Revised Label – Section 17

Inform patients that the use of BUTRANS, even when taken as recommended, can result in addiction, abuse, and misuse, which could lead to overdose and death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share BUTRANS with others and to take steps to protect BUTRANS from theft or misuse.

III. December 16, 2016

1. There was a change in language in the **Dosage and Administration** in the **Highlights of Prescribing Information**.

4/2014 Revised Label – Dosage and Administration in Highlights of Prescribing Information

BUTRANS doses of 7.5, 10, 15, and 20 mcg/hour are for opioid-experienced patients only. (2.1)

For opioid-naïve patients, initiate with a 5 mcg/hour patch. (2.1)

Instruct patients to wear BUTRANS for 7 days and to wait a minimum of 3 weeks before applying to the same site. (2.1)

12/2016 Revised Label – Dosage and Administration in Highlights of Prescribing Information

To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)

BUTRANS doses of 7.5, 10, 15, and 20 mcg/hour are only for use in patients who are opioid experienced and in whom tolerance to an opioid of comparable potency has been established. Patients who are opioid-experienced are those receiving, for one week or longer, daily opioid doses up to 80 mg/day of oral morphine or an equianalgesic dose of another opioid. (2.1)

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).

Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)

- For opioid-naïve patients, initiate treatment with a 5 mcg/hour patch. (2.1)
- Instruct patients to wear BUTRANS for 7 days and to wait a minimum of 3 weeks before applying to the same site. (2.1)

2. In **Section 2.1 Dosage and Administration** the following sentence was added: “[u]se the lowest effective dosage for the shortest duration consistent with individual patients treatment goals [*see Warnings and Precautions (5)*].

3. **Section 2.3 Cessation of Therapy** was changed to **Section 2.4 Discontinuation of BUTRANS** with a change in language.

4/2014 Revised Label – Section 2.3

When the patient no longer requires therapy with BUTRANS, use a gradual downward titration of the dose every 7 days to prevent signs and symptoms of withdrawal in the physically dependent patient; consider introduction of an appropriate immediate-release opioid medication. Do not abruptly discontinue BUTRANS.

12/2016 Revised Label – Section 2.4

When the patient no longer requires therapy with BUTRANS, use a gradual downward titration of the dose every 7 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, consider introduction of an appropriate immediate-release opioid medication. Do not abruptly discontinue BUTRANS.

4. The language in **Section 9.1 Controlled Substance** was moved to **Section 9.2 Abuse**. The new **9.1 Controlled Substance** reads as follows:
“BUTRANS contains buprenorphine, a Schedule III controlled substance.”

5. The below language had a change in language in **Section 9.2 Abuse**.

4/2014 Revised Label – Section 9.2

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects.

12/2016 Revised Label – Section 9.2 language changed

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

6. The below language was added to **Section 9.2 Abuse**.

12/2016 Revised Label – Section 9.2 language added

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

7. The below language was removed from **Section 9.2 Abuse**.

4/2014 Revised Label – Section 9.2 language removed

Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

ENDO
LABEL CHANGES FOR PERCOCET
(ANDA 085106, 040330, 040341)

SUMMARY OF LABEL CHANGES

The FDA approved ANDA 085106 for Percocet 5mg/325mg on August 31, 1976. The initial label is not available either from Defendants' production or from the FDA website, so the indication and warning sections from the 1988 label are included for reference. FDA approved Endo's ANDAs 040330 and 040341 on June 26, 1999 and July 26, 1999, respectively.

- I. April 1988 First Available Label**⁶
 1. Indication in **INDICATIONS AND USAGE** section of the first available label for Percocet. [no change]
 2. Language in the **WARNINGS** section of the first available label for Percocet. [no change]
 3. Language reflecting the established name and statement of equivalency added to the **DESCRIPTION** section.
 4. New language added to the **OVERDOSAGE/Acetaminophen/Signs and Symptoms** section.
- II. June 26, 1999 ANDA 040330 Initial Approval of ANDA 040341**⁷
 1. Endo's ANDA 040330 for Percocet 2.5mg and 5mg approved.
 2. The term "narcotic-containing" was replaced with "opioid-containing" in the **WARNINGS/ Drug Dependence** section.
- III. July 26, 1999 Initial Approval of ANDA 040341**⁸
 1. Endo's ANDA 040341 for Percocet 7.5mg and 10mg approved.
- IV. March 16, 2004**
 1. Unified all strengths of Percocet - 2.5mg/325mg, 5mg/325mg, 7.5mg/325mg, 7.5mg/500mg, 10mg/325mg and 10mg/650mg – under the same label.
- V. November 2006**⁹
 1. New language added to the **CONTRAINDICATIONS** section.
 2. The Drug Dependence subsection in **WARNINGS** was replaced with a Misuse, Abuse and Diversion of Opioids subsection.
 3. The language in the **DRUG ABUSE AND DEPENDENCE** section was significantly expanded.
- VI. June 28-29, 2011**¹⁰

⁶ ENDO-OPIOID_MDL-05411641; *see also* the 1989 PDR.

⁷ ENDO-OPIOID_MDL-04640430; https://www.accessdata.fda.gov/drugsatfda_docs/anda/99/40-330_Oxycodone%20and%20Acetaminophen.pdf at 5.

⁸ https://www.accessdata.fda.gov/drugsatfda_docs/anda/99/40-341_Oxycodone%20And%20Acetaminophen.pdf.

⁹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/040330s015,040341s013,040434s003lbl.pdf (NDA 040330);

https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/040330s015,040341s013,040434s003lbl.pdf (NDA 040341).

1. First **Boxed Warning** added for Hepatotoxicity.
2. Hepatotoxicity and hypersensitivity/anaphylaxis added to the **WARNINGS** section.
3. New language added to the **INFORMATION FOR PATIENTS/CAREGIVERS** section.
4. The **OVERDOSAGE** section was replaced almost in its entirety.

VII. April 10, 2012¹¹

1. Revision to format and layout of PERCOCET container label.

VIII. October 18, 2013¹²

1. Serious skin reactions added to the **WARNINGS** section.

IX. December 16, 2016¹³

1. The **INDICATIONS AND USAGE** section revised to narrow Percocet indication.
2. New language pertaining to misuse/abuse/addiction/overdose/death, neonatal opioid withdrawal syndrome, serotonin syndrome, adrenal insufficiency, androgen deficiency, as well as the serious risks of profound sedation, respiratory depression, coma, and death associated with concomitant use of opioid analgesics and benzodiazepines added to **WARNINGS** section.
3. New language added to the **PRECAUTIONS** section.

X. September 2018

1. Details about REMS added to the **Boxed Warning**.
2. Details about REMS added to the **WARNINGS** section.

¹⁰ ENDO-OPIOID_MDL-05522714; ENDO-OPIOID_MDL-05522829.

¹¹ ENDO-OPIOID_MDL-05529268.

¹² ENDO-OPIOID_MDL-05532555.

¹³ ENDO-OPIOID_MDL-01806106; *see also* ENDO-OPIOID_MDL-05539726.

DETAILED REVIEW OF LABEL CHANGES

I. April 1988 First Available Label

1. Indication in **INDICATIONS AND USAGE** section of the first available label for Percocet.

1988 Package Insert
PERCOCET is indicated for the relief of moderate to moderately severe pain.

2. Language in the **WARNINGS** section of the first available label for Percocet.

1988 Package Insert
Drug Dependence: Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET is subject to the Federal Controlled Substances Act (Schedule II).

3. Language reflecting the established name and statement of equivalency added to the **DESCRIPTION** section.

1988 Package Insert
"+5 mg oxycodone hydrochloride is equivalent to 4.48/5 mg of oxycodone."

4. New language added to the **OVERDOSAGE/Acetaminophen/Signs and Symptoms** section.

1988 Package Insert
"In acute acetaminophen overdosage, dose -dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur."

II. June 26, 1999 Initial Approval of ANDA 040330

1. Endo's ANDA 040330 for Percocet 2.5mg and 5mg approved.

2. The term “narcotic-containing” was replaced with “opioid-containing” in the **WARNINGS/ Drug Dependence** section.

1988 Package Insert

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type and the potential for being abused. Psychic dependence, physical dependence and tolerance upon repeated administration of PERCOCET, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. PERCOCET is subject to the Federal Controlled Substance Act (Schedule II).

June 1999 Package Insert

WARNINGS

Drug Dependence: Oxycodone can produce drug dependence of the morphine type and therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral opioid-containing medications. Like other opioid-containing medications, PERCOCET is subject to the Federal Controlled Substances Act (Schedule II).

III. July 26, 1999 Initial Approval of ANDA 040341

1. Endo's ANDA 040341 for Percocet 7.5mg and 10mg approved.

IV. March 16, 2004

2. Unified all strengths of Percocet - 2.5mg/325mg, 5mg/325mg, 7.5mg/325mg, 7.5mg/500mg, 10mg/325mg and 10mg/650mg – under the same label.

1999 Package Insert

DESCRIPTION

Each tablet, for oral administration, contains oxycodone hydrochloride and acetaminophen in the following strengths:

Oxycodone Hydrochloride	2.5 mg*
Acetaminophen, USP	325 mg

Oxycodone Hydrochloride	5 mg*
Acetaminophen, USP	325 mg

* 2.5 mg oxycodone HCl is equivalent to 2.2409 mg of oxycodone.
5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.

2004 Physicians' Desk Reference

DESCRIPTION	
Each tablet, for oral administration, contains oxycodone hydrochloride and acetaminophen in the following strengths:	
Oxycodone Hydrochloride, USP	2.5 mg
Acetaminophen, USP	325 mg
2.5 mg oxycodone HCl is equivalent to 2.2409 mg of oxycodone.	
Oxycodone Hydrochloride, USP	5 mg
Acetaminophen, USP	325 mg
5 mg oxycodone HCl is equivalent to 4.4815 mg of oxycodone.	
Oxycodone Hydrochloride, USP	7.5 mg
Acetaminophen, USP	325 mg
7.5 mg oxycodone HCl is equivalent to 6.7228 mg of oxycodone.	
Oxycodone Hydrochloride, USP	7.5 mg
Acetaminophen, USP	500 mg
7.5 mg oxycodone HCl is equivalent to 6.7228 mg of oxycodone.	
Oxycodone Hydrochloride, USP	10 mg
Acetaminophen, USP	325 mg
10 mg oxycodone HCl is equivalent to 8.9637 mg of oxycodone.	
Oxycodone Hydrochloride, USP	10 mg
Acetaminophen, USP	650 mg

V. November 2006

1. New language added to the **CONTRAINDICATIONS** section.

2006 Package Insert
<p>“Oxycodone is contraindicated in any situation where opioids are contraindicated including patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment) and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone is contraindicated in the setting of suspected or known paralytic ileus.”</p>

2. The Drug Dependence subsection in **WARNINGS** was replaced with a Misuse, Abuse and Diversion of Opioids subsection.

2006 Package Insert
<p>Misuse, Abuse and Diversion of Opioids</p> <p>Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing PERCOCET tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Concerns about misuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent</p>

and detect abuse or diversion of this product. Administration of PERCOCET (Oxycodone and Acetaminophen Tablets, USP) should be closely monitored for the following potentially serious adverse reactions and complications:

Respiratory depression was added to the WARNINGS for Percocet:

Respiratory depression is a hazard with the use of oxycodone, one of the active ingredients in PERCOCET tablets, as with all opioid agonists. Elderly and debilitated patients are at particular risk for respiratory depression as are non-tolerant patients given large initial doses of oxycodone or when oxycodone is given in conjunction with other agents that depress respiration. Oxycodone should be used with extreme caution in patients with acute asthma, chronic obstructive pulmonary disorder (COPD), cor pulmonale, or preexisting respiratory impairment. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose. In case of respiratory depression, a reversal agent such as naloxone hydrochloride may be utilized (see OVERDOSAGE).

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of worsening in patients with head injuries.

Hypotensive Effect: Oxycodone may cause severe hypotension particularly in individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs which compromise vasomotor tone such as phenothiazines. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure. Oxycodone may produce orthostatic hypotension in ambulatory patients.

Hepatotoxicity: Precaution should be taken in patients with liver disease. Hepatotoxicity and severe hepatic failure occurred in chronic alcoholics following therapeutic doses.

3. The language in the **DRUG ABUSE AND DEPENDENCE** section was significantly expanded.

2004 Physicians' Desk Reference

DRUG ABUSE AND DEPENDENCE

PERCOCET (Oxycodone and Acetaminophen Tablets, USP) is a Schedule II controlled substance.

Oxycodone can produce drug dependence and has the potential for being abused (See WARNINGS).

2006 Package Insert

DRUG ABUSE AND DEPENDENCE

PERCOCET tablets are a Schedule II controlled substance. Oxycodone is a mu-agonist opioid with an abuse liability similar to morphine. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is defined as an abnormal, compulsive use, use for non-medical purposes of a substance despite physical, psychological, occupational or interpersonal difficulties resulting from such use, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common. Opioid addiction is relatively rare in patients with chronic pain but may be more common in individuals who have a past history of alcohol or substance abuse or dependence. Pseudoaddiction refers to pain relief seeking behavior of patients whose pain is poorly managed. It is considered an iatrogenic effect of ineffective pain management. The health care provider must assess continuously the psychological and clinical condition of a pain patient in order to distinguish addiction from pseudoaddiction and thus, be able to treat the pain adequately.

Physical dependence on a prescribed medication does not signify addiction. Physical dependence involves the occurrence of a withdrawal syndrome when there is sudden reduction or cessation in drug use or if an opiate antagonist is administered. Physical dependence can be detected after a few days of opioid therapy. However, clinically significant physical dependence is only seen after several weeks of relatively high dosage therapy. In this case, abrupt discontinuation of the opioid may result in a withdrawal syndrome. If the discontinuation of opioids is therapeutically indicated, gradual tapering of the drug over a 2-week period will prevent withdrawal symptoms. The severity of the withdrawal syndrome depends primarily on the daily dosage of the opioid, the duration of therapy and medical status of the individual.

The withdrawal syndrome of oxycodone is similar to that of morphine. This syndrome is characterized by yawning, anxiety, increased heart rate and blood pressure, restlessness, nervousness, muscle aches, tremor, irritability, chills alternating with hot flashes, salivation, anorexia, severe sneezing, lacrimation, rhinorrhea, dilated pupils, diaphoresis, piloerection, nausea, vomiting, abdominal cramps, diarrhea and insomnia, and pronounced weakness and depression.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor Shopping" to obtain additional prescriptions is common among drug abusers and people suffering

from untreated infection.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Oxycodone, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Like other opioid medications, PERCOCET tablets are subject to the Federal Controlled Substances Act. After chronic use, PERCOCET tablets should not be discontinued abruptly when it is thought that the patient has become physically dependent on oxycodone.

VI. June 28-29, 2011

1. First **Boxed Warning** added for Hepatotoxicity.

2011 Package Insert**“Hepatotoxicity**

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product.”

2. Hepatotoxicity and hypersensitivity/anaphylaxis added to the **WARNINGS** section.

2011 Package Insert**“Hepatotoxicity**

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products. The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen. Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4000 milligrams of acetaminophen per day, even if they feel well.”

“Hypersensitivity/anaphylaxis

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue PERCOCET immediately and seek medical care if they experience these symptoms. Do not prescribe PERCOCET for patients with acetaminophen allergy.”

3. New language added to the **INFORMATION FOR PATIENTS/CAREGIVERS** section.

2011 Package Insert

1. Do not take PERCOCET if you are allergic to any of its ingredients.
2. If you develop signs of allergy such as a rash or difficulty breathing stop taking PERCOCET and contact your healthcare provider immediately.
3. Do not take more than 4000 milligrams of acetaminophen per day. Call your doctor if you took more than the recommended dose.

4. The **OVERDOSAGE** section was replaced almost in its entirety (language retained from prior label is underlined).

2011 Package Insert

OVERDOSAGE

Following an acute overdose toxicity may result from the oxycodone or the acetaminophen.

Signs and Symptoms

Toxicity from oxycodone poisoning includes the opioid triad of: pinpoint pupils, depression of respiration, and loss of consciousness. Serious overdose with oxycodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest, and death may occur. In acetaminophen overdose, dose-dependent potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment

A single or multiple drug overdose with oxycodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered.

Oxycodone

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist

naloxone hydrochloride is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone.). Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance, and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Acetaminophen:

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration. Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

VII. April 10, 2012

1. Revision to format and layout of PERCOCET container label.

VIII. October 18, 2013

1. Serious skin reactions added to the **WARNINGS** section.

2013 Package Insert

“Serious Skin Reactions

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.”

IX. December 16, 2016

1. The **INDICATIONS AND USAGE** section revised to narrow Percocet indication.

2016 Package Insert

PERCOCET is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use: Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses [see WARNINGS], reserve PERCOCET for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]

- Have not been tolerated, or are not expected to be tolerated.
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

2. New warnings added to Percocet **Boxed Warning**.

2013 Package Insert

WARNING

Hepatotoxicity

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product.

2016 Package Insert

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME, CYTOCHROME P450 3A4 INTERACTION; HEPATOTOXICITY, and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

PERCOCET exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing PERCOCET and monitor all patients regularly for the development of these behaviors and conditions [see WARNINGS].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of PERCOCET. Monitor for respiratory depression, especially during initiation of PERCOCET or following increase [see WARNINGS].

Accidental Ingestion

Accidental ingestion of PERCOCET, especially by children, can result in a fatal overdose of PERCOCET [see WARNINGS].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of PERCOCET during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see WARNINGS].

Cytochrome P450 3A4 Interaction

The concomitant use of PERCOCET with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving PERCOCET and any CYP3A4 inhibitor or inducer [see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions].

Hepatotoxicity

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen doses that exceed 4000 mg per day, and often involve more than one acetaminophen-containing product.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings, Precautions: Drug Interactions].

Reserve concomitant prescribing of PERCOCET and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.

Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation.

3. New language pertaining to misuse/abuse/addiction/overdose/death, neonatal opioid withdrawal syndrome, serotonin syndrome, adrenal insufficiency, androgen deficiency, as well as the serious risks of profound sedation, respiratory depression, coma, and death associated with concomitant use of opioid analgesics and benzodiazepines added to **WARNINGS** section.

2016 Package Insert

WARNINGS

Addiction, Abuse, and Misuse

PERCOCET contains oxycodone, a Schedule II controlled substance. As an opioid, PERCOCET exposes users to the risks of addiction, abuse, and misuse [see DRUG ABUSE AND DEPENDENCE].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed PERCOCET. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing PERCOCET and monitor all patients receiving PERCOCET for the development of these behaviors and conditions. Risk factors for addiction, abuse, or misuse include: a history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk of addiction, abuse, or misuse who are prescribed opioids such as PERCOCET, but use in such patients necessitates intensive counseling about the risks and proper use of PERCOCET along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing PERCOCET. Strategies to reduce risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see PRECAUTIONS; Information for Patients/Caregivers]. Consult your local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see OVERDOSAGE]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of PERCOCET, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiation with and following dosage increases of PERCOCET.

To reduce the risk of respiratory depression, proper dosing and titration of PERCOCET are essential [see DOSAGE AND ADMINISTRATION]. Overestimating the PERCOCET dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of PERCOCET, especially by children, can result in respiratory depression and death due to an overdose of PERCOCET.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of PERCOCET during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see PRECAUTIONS; Information for Patients/Caregivers, Pregnancy].

Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of PERCOCET with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone hydrochloride and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [see Warnings], particularly when a CYP3A4 inhibitor is added after a stable dose of PERCOCET is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in PERCOCET-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using PERCOCET with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in PERCOCET-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of PERCOCET until stable drug effects are achieved [see PRECAUTIONS; Drug Interactions].

Concomitant use of PERCOCET with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease oxycodone hydrochloride plasma concentrations, decrease opioid efficacy or

lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone hydrochloride. When using PERCOCET with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if not able to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see PRECAUTIONS: Drug Interactions].

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of PERCOCET with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics /see PRECAUTIONS; Drug Interactions.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. For all patients, monitor closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when PERCOCET is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or Elderly, Cachectic, or Debilitated Patients

The use of PERCOCET in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: PERCOCET-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of life-threatening respiratory depression, even at recommended dosages of PERCOCET [see WARNINGS: Life-Threatening Respiratory Depression].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or

clearance compared to younger, healthier patients [see WARNINGS; Life Threatening Respiratory Depression].

Monitor such patients closely, particularly when initiating and titrating PERCOCET and when PERCOCET is given concomitantly with other drugs that depress respiration [see WARNING; Life Threatening Respiratory Depression]. Alternatively, consider the use of non-opioid analgesics in these patients.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioid being more likely to be associated with adrenal insufficiency.

Severe Hypotension

PERCOCET may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [see PRECAUTIONS; Drug Interactions]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of PERCOCET. In patients with circulatory shock PERCOCET may cause vasodilatation that can further reduce output and blood pressure. Avoid the use of PERCOCET with circulatory shock.

Hepatotoxicity

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplantation and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional due to patients' attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4000 milligrams of acetaminophen per day, even if they feel well.

Serious Skin Reactions

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hypersensitivity/Anaphylaxis

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue PERCOCET immediately and seek medical care if they experience these symptoms. Do not prescribe PERCOCET for patients with acetaminophen allergy [see PRECAUTIONS; Information for Patients/Caregivers].

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with a history of increased intracranial pressure or brain tumors), PERCOCET may reduce respiratory drive, and resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with PERCOCET.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of PERCOCET in patients with impaired consciousness or coma.

Risks of Use in Patients with Gastrointestinal Conditions

PERCOCET are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The administration of PERCOCET, or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

The oxycodone in PERCOCET may cause spasm of the sphincter of Oddi. Opioids may cause an increase in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in PERCOCET may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizure disorders. Monitor patients with a history of seizure disorders for worsened seizure control during PERCOCET therapy.

Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including PERCOCET. In these patients, mixed agonist/antagonist and partial agonists may precipitate withdrawal symptoms.

analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing PERCOCET, gradually taper the dosage [see DOSAGE AND ADMINISTRATION]. Do not abruptly discontinue PERCOCET [see DRUG ABUSE AND DEPENDENCE].

Risks of Driving and Operating Machinery

PERCOCET may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate machinery unless they are tolerant to the effects of PERCOCET and know how they will react to medication [see PRECAUTIONS; Information for Patients/Caregivers].

4. New language added to the **PRECAUTIONS** section.

2016 Package Insert

PRECAUTIONS

Information for Patients/Caregivers

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse, and Misuse

Inform patients that the use of PERCOCET, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see WARNINGS]. Instruct patients not to share PERCOCET with others and to take steps to protect PERCOCET from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting PERCOCET or when the dosage is increased, and that it can occur even at recommended dosages [see WARNINGS]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression and death [see WARNINGS]. Instruct patients to take steps to store PERCOCET securely and to dispose of unused PERCOCET by flushing tablets down the toilet. In the case of accidental ingestions, emergency medical care should be sought immediately.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if PERCOCET is used with benzodiazepines and other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider [see WARNINGS, PRECAUTIONS; Drug Interactions].

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications [see PRECAUTIONS; Drug Interactions].

Monoamine Oxidase Inhibitor (MAOI) Interaction

Inform patients to avoid taking PERCOCET using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking PERCOCET Tablets [see PRECAUTIONS; Drug Interactions].

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see WARNINGS].

Important Administration Instructions

Instruct patients how to properly take PERCOCET (see **DOSAGE AND ADMINISTRATION** and **WARNINGS**).

Advise patients not to adjust the medication dose themselves and to consult with their healthcare provider prior to any dosage adjustment.

Advise patients who are treated with PERCOCET for more than a few weeks not to abruptly discontinue the medication. Advise patients to consult with their physician for a gradual discontinuation of the dose schedule to taper off the medication.

Maximum Daily Dose of Acetaminophen

Inform patients to not take more than 4000 milligrams of acetaminophen per day. Advise patients to call their prescriber if they take more than the recommended dose.

Hypotension

Inform patients that PERCOCET may cause orthostatic hypotension and syncope. Instruct patients to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see WARNINGS].

Anaphylaxis

Inform patients that anaphylaxis have been reported with ingredients contained in PERCOCET. Advise patients how to recognize such a reaction and when to seek medical attention [see CONTRAINDICATIONS, ADVERSE REACTIONS].

Pregnancy

Neonatal Opioid Withdrawal Syndrome Inform female patients of reproductive potential that prolonged use of PERCOCET during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see WARNINGS, PRECAUTIONS; Pregnancy].

Embryo-Fetal Toxicity Inform female patients of reproductive potential that PERCOCET may cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy [see PRECAUTIONS; Pregnancy].

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice signs [see PRECAUTIONS; Nursing Mothers].

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether

effects on fertility are reversible [see ADVERSE REACTIONS].

Driving or Operating Heavy Machinery

Inform patients that PERCOCET may impair the ability to perform potentially hazardous tasks such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see PRECAUTIONS].

Constipation

Advise patients of the potential for severe constipation, including management instructions to seek medical attention [see ADVERSE REACTIONS, CLINICAL PHARMACOLOGY].

Disposal of Unused PERCOCET Advise patients to dispose of unused PERCOCET by flushing tablets down the toilet.

Laboratory Tests

Although oxycodone may cross-react with some drug urine tests, no available studies were determined the duration of detectability of oxycodone in urine drug screens. However, based on pharmacokinetic data, the approximate duration of detectability for a single dose of oxycodone is estimated to be one to two days following drug exposure.

Urine testing for opiates may be performed to determine illicit drug use and for medical reevaluation of patients with altered states of consciousness or monitoring efficacy of drug rehabilitation efforts. The preliminary identification of opiates in urine involves the use of an immunoassay and thin-layer chromatography (TLC). Gas chromatography/mass spectrometry (GC/MS) is utilized as a third-stage identification step in the medical investigational sequence for opiate identification. The identities of 6-keto opiates (e.g., oxycodone) can further be determined by the analysis of their methoxymethyltrimethylsilyl (MO-TMS) derivative.

Drug Interactions

Inhibitors of CYP3A4 and CYP2D6

The concomitant use of PERCOCET and CYP3A4 inhibitors, such as macrolide antibiotic (erythromycin), azole-antifungal agents (e.g. ketoconazole), and protease inhibitors (e.g., ritonavir) increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of PERCOCET and CYP3A4 and CYP2D6 inhibitors, particularly when an inhibitor is added after a stable dose of PERCOCET has been achieved [see WARNINGS].

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease [see CLINICAL PHARMACOLOGY], resulting in decreased opioid effects or a withdrawal syndrome in patients who had developed physical dependence to PERCOCET.

If concomitant use is necessary, consider dosage reduction of PERCOCET until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If the inhibitor is discontinued, consider increasing the PERCOCET dosage until stable drug effects are achieved.

Monitor for signs of opioid withdrawal.

Inducers of CYP3A4

The concomitant use of PERCOCET and CYP3A4 inducers, such as rifampin, carbamazepine, phenytoin, can decrease the plasma concentration of oxycodone [see CLINICAL PHARMACOLOGY], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to PERCOCET [see WARNINGS].

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase [see CLINICAL PHARMACOLOGY], which could increase or prolong the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

If concomitant use is necessary, consider increasing the PERCOCET dosage until stable drug effect is achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider PERCOCET dosage reduction and monitor for signs of respiratory depression.

Benzodiazepines and Other CNS Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines and other CNS depressants such as benzodiazepines and other sedative hypnotics, anxiolytics, and tranquilizers, relaxants, general anesthetics, antipsychotics, and other opioids, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatments are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see WARNINGS].

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter systems, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tryptans, 5-HT₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome. [see PRECAUTIONS Information for Patients/Caregivers].

If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue PERCOCET if serotonin syndrome is suspected.

Monoamine Oxidase Inhibitors (MAOIs)

The concomitant use of opioids and MAOIs, such as phenelzine, tranylcypromine, linezolid, may result in serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see WARNINGS].

The use of PERCOCET is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

The concomitant use of opioids with other opioid analgesics, such as butorphanol, nalbuphine, pentazocine, may reduce the analgesic effect of PERCOCET and/or precipitate withdrawal symptoms.

Advise patient to avoid concomitant use of these drugs.

Muscle Relaxants

PERCOCET may enhance the neuromuscular-blocking action of skeletal muscle relaxants and increase the degree of respiratory depression.

If concomitant use is warranted, monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of PERCOCET and/or the muscle relaxant as necessary.

Diuretics

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

If concomitant use is warranted, monitor patients for signs of diminished diuresis and/or effective blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic Drugs

The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

If concomitant use is warranted, monitor patients for signs of urinary retention or reduced gastric motility when PERCOCET is used concomitantly with anticholinergic drugs.

Alcohol, ethyl

Hepatotoxicity has occurred in chronic alcoholics following various dose levels (moderate to high) of acetaminophen.

Oral Contraceptives

Increase in glucuronidation resulting in increased plasma clearance and a decreased half-life of acetaminophen.

Charcoal (activated)

Reduces acetaminophen absorption when administered as soon as possible after overdose.

Beta Blockers (Propranolol)

Propranolol appears to inhibit the enzyme systems responsible for the glucuronidation and oxidation of acetaminophen. Therefore, the pharmacologic effects of acetaminophen may be increased.

Loop Diuretics

The effects of the loop diuretic may be decreased because acetaminophen may decrease renal prostaglandin excretion and decrease plasma renin activity.

Lamotrigine

Serum lamotrigine concentrations may be reduced, producing a decrease in therapeutic effect.

Probenecid

Probenecid may increase the therapeutic effectiveness of acetaminophen slightly.

Zidovudine

The pharmacologic effects of zidovudine may be decreased because of enhanced non-hepatic or clearance of zidovudine

Drug/Laboratory Test Interactions

Depending on the sensitivity/specificity and the test methodology, the individual components of PERCOCET may cross-react with assays used in the preliminary detection of cocaine (primary metabolite, benzoylecgonine) or marijuana (cannabinoids) in human urine. A more specific analytical chemical method must be used in order to obtain a confirmed analytical result. The preferred confirmatory method is gas chromatography/mass spectrometry (GC/MS). Moreover, clinical considerations and professional judgment should be applied to any drug-of-abuse test result, particularly when preliminary positive results are used.

Acetaminophen may interfere with home blood glucose measurement systems; decreases of >20% in mean glucose values may be noted. This effect appears to be drug, concentration and system dependent.

Carcinogenesis, Mutagenesis, Impairment of Fertility**Carcinogenesis**

Long-term studies to evaluate the carcinogenic potential of the combination of Oxycodone Hydrochloride and Acetaminophen have not been conducted.

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F₁ mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats that received up to 0.7 times at up to 1.2-1.4 times the MHDD, based on a body surface area comparison.

Mutagenesis

The combination of Oxycodone Hydrochloride and Acetaminophen has not been evaluated for mutagenicity. Oxycodone alone was negative in a bacterial reverse mutation assay (Ames), an chromosome aberration assay with human lymphocytes without metabolic activation and an *in vivo* mouse micronucleus assay. Oxycodone was clastogenic in the human lymphocyte chromosome assay in the presence of metabolic activation and in the mouse lymphoma assay with or without metabolic activation.

In the published literature, acetaminophen has been reported to be clastogenic when administered at 750 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In the mouse, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Impairment of Fertility

In studies conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss CD-1 mice via a continuous breeding study. There were no effect on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.78 times the MHDD (based on a body surface comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses 1.2 times the MHDD and greater (based on a body surface comparison) result in decreased testis weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see ADVERSE REACTIONS].

Pregnancy

Teratogenic Effects

Pregnancy Category C

Animal reproductive studies have not been conducted with PERCOCET. It is also not known whether PERCOCET can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. PERCOCET should not be given to a pregnant woman unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Nonteratogenic Effects

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see WARNINGS].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced effects.

respiratory depression in the neonate. PERCOCET is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including PERCOCET, can prolong labor through actions which temporarily reduce uterine strength, duration, and frequency of uterine contractions. However, this effect is not consistently offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Nursing Mothers

Ordinarily, nursing should not be undertaken while a patient is receiving PERCOCET because of the possibility of sedation and/or respiratory depression in the infant. Oxycodone is excreted in breast milk in low concentrations, and there have been rare reports of somnolence and lethargy in babies of nursing mothers taking an oxycodone/acetaminophen product. Acetaminophen is also excreted in breast milk in low concentrations.

The developmental and health benefits of breastfeeding should be considered along with the maternal clinical need for PERCOCET and any potential adverse effects on the breastfed infant from PERCOCET or from the underlying maternal condition.

Infants exposed to PERCOCET through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

Pediatric Use

Safety and effectiveness of PERCOCET in pediatric patients have not been established.

Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to PERCOCET. In general, exercise caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred following large initial doses were administered to patients who were not opioid-tolerant or when opioids were administered with other agents that depress respiration. Titrate the dosage of PERCOCET slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression. [See WARNINGS].

These drugs are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be prudent to monitor renal function.

Hepatic Impairment

In a pharmacokinetic study of oxycodone in patients with end-stage liver disease, oxycodone plasma clearance decreased and the elimination half-life increased.

Because oxycodone is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. Initiate therapy in these patients with a lower than usual dosage of PERCOCET and titrate carefully. Monitor closely for adverse events such as respiratory depression, sedation, hypotension [see Clinical Pharmacology].

Renal Impairment

In a study of patients with end stage renal impairment, mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance. Oxycodone should be used with caution in patients with renal impairment.

Because oxycodone is known to be substantially excreted by the kidney, its clearance may be decreased in patients with renal impairment. Initiate therapy with a lower than usual dosage of PERCOCET and titrate carefully. Monitor closely for adverse events such as respiratory depression, sedation, hypotension [see Clinical Pharmacology].

X. September 2018

1. Details about REMS added to the **Boxed Warning.**

2018 Package Insert

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [see WARNINGS]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

2. Details about REMS added to the **WARNINGS** section.

2018 Package Insert

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, dmj companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Prescribers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link:
www.fda.gov/OpioidAnalgesicREMSPCD.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

ENDO
LABEL CHANGES FOR OPANA ER
(NDA 021610)

SUMMARY OF LABEL CHANGES

- I. **June 26, 2006 Initial Label**¹⁴
- II. **August 2, 2006**¹⁵
 1. Language regarding incidence of addiction was deleted from the **WARNINGS/Misuse, Abuse and Diversion of Opioids** section.
- III. **July 9, 2007**¹⁶
 1. New language regarding opioid conversion added to the **DOSAGE AND ADMINISTRATION/Initiation of Therapy/ Conversion from Other Oral Opioids to OPANA ER** section
- IV. **January 10, 2008**¹⁷
 1. Change to appearance of the tablets.
- V. **February 29, 2008**¹⁸
 1. New strengths added.
- VI. **October 4, 2010**¹⁹
 1. The package insert was converted into the Physicians Labeling Rule (PLR) format.
- VII. **July 9, 2012**²⁰
 - FDA approved ER/LA Opioid Class REMS and standardized the package inserts for all ER/LA opioids.
 - The language in **boxed warning** changed
 - The limitation of usage language in the **INDICATION AND USAGE** section changed.
 - The language in **DOSAGE AND ADMINISTRATION** section was redrafted, but no substantive changes were made.
 - New language on abuse potential added to the **WARNINGS AND PRECAUTIONS** section.
 - Warning about respiratory depression in **WARNINGS AND PRECAUTIONS** was replaced with a warning of life threatening respiratory depression.
 - Accidental exposure warning added to the **WARNINGS AND PRECAUTIONS** section.

¹⁴ ENDO-CHI_LIT-00546939.

¹⁵ ENDO-OPIOID_MDL-00299009 (supplement requesting this change); *see also* https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021610s001,021611s001lbl.pdf (changed label).

¹⁶ ENDO-OPIOID_MDL-00541870.

¹⁷ ENDO-OPIOID_MDL-00300267 (NDA Supplement submitted by Endo); *see also* https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021610s0051bl.pdf (the new label).

¹⁸ ENDO-OPIOID_MDL-00076365.

¹⁹ EPI000387498.

²⁰ END00546201.

- Section 5.4 Interactions with Alcohol and other CNS Depressants in **WARNINGS AND PRECAUTIONS** section was replaced with two sections, Section 5.4 Interaction with Alcohol and Section 5.7 Interactions with CNS Depressants and Illicit Drugs.
- New section 5.5 Elderly, Cachectic, and Debilitated Patients was added to the **WARNINGS AND PRECAUTIONS** section.
- A new Section 5.13 Avoidance of Withdrawal was added to **WARNINGS AND PRECAUTIONS** section.
- New language added to **ADVERSE REACTION/Post-marketing Experience** section.

VIII. April 16, 2014²¹

1. The Abuse Potential warning in **Boxed Warnings** was replaced with an Addiction, Abuse, and Misuse warning.
2. New warning regarding Neonatal Opioid Withdrawal Syndrome added to the **Boxed Warnings**.
3. The indication in **INDICATIONS AND USAGE** section was narrowed to severe pain for which other treatment options are inadequate.
4. New language added to **DOSAGE AND ADMINISTRATION/Initial Dosing** section.
5. A new subsection added to **DOSAGE AND ADMINISTRATION/Initial Dosing** section.
6. Changes made to the addiction abuse and misuse language in the **WARNINGS AND PRECAUTIONS** section.
7. A new warning regarding the risk of Neonatal Opioid Withdrawal Syndrome was added to the **WARNINGS AND PRECAUTIONS** section.

IX. December 16, 2016²²

- Risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants added to the **Boxed Warning**.
- A new subsection added to **DOSAGE AND ADMINISTRATION** section.
- The language in Subsection 2.4 Discontinuation of OPANA ER in **DOSAGE AND ADMINISTRATION** changed.
- Language describing symptoms of Neonatal Opioid Withdrawal was deleted from **WARNINGS AND PRECAUTIONS/Neonatal Opioid Withdrawal Syndrome** section.
- Subsection 5.4 Interactions with Central Nervous System Depressants Risks in **WARNINGS AND PRECAUTIONS** section was replaced with subsection 5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants.
- A new section regarding risk of Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions added to the **WARNINGS AND PRECAUTIONS** section.

²¹ ENDO-OPIOID_MDL-00020264.

²² ENDO-OPIOID_MDL-00073281.

- A new section Adrenal Insufficiency added to **RISKS AND PRECAUTIONS** section.

X. September 19, 2018²³

1. Information about REMS added to the **Boxed Warning**.
2. Information about the REMS added to the **WARNINGS AND PRECAUTIONS** section.

²³ https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021610s025s026lbl.pdf.

DETAILED REVIEW OF LABEL CHANGES

I. June 26, 2006 Initial Label

1. Approved **INDICATION AND USAGE**.

June 2006 Package Insert
<p>OPANA ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. OPANA ER is not intended for use as a prn analgesic. OPANA ER is not indicated for pain in the immediate post-operative period (12-24 hours following surgery) for patients not previously taking opioids because of the risk of oversedation and respiratory depression requiring reversal with opioid antagonists. OPANA ER is not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.</p>

2. Approved **Boxed Warning**.

June 2006 Package Insert
<p>WARNING:</p> <p>OPANA ER contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.</p> <p>Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.</p> <p>OPANA ER is an extended-release oral formulation of oxymorphone indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.</p> <p>OPANA ER is NOT intended for use as a prn analgesic.</p> <p>OPANA ER TABLETS are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed OPANA ER TABLETS leads to rapid release and absorption of a potentially fatal dose of oxymorphone.</p> <p>Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.</p>

II. August 2, 2006

1. Language was deleted from the **WARNINGS/Misuse, Abuse and Diversion of Opioids** section.

August 2006 Package Insert

~~“The development of addiction to opioid analgesia in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.”~~

III. July 9, 2007

1. New language added to the **DOSAGE AND ADMINISTRATION/Initiation of Therapy/ Conversion from Other Oral Opioids to OPANA ER** section.

2007 Package Insert

The conversion ratios and approximate equivalent doses in this conversion table are only to be used for the conversion from current opioid therapy to OPANA ER.

IV. January 10, 2008

1. Change in the code imprint for all strengths of OPANA ER Tablets from black ink imprinting to debossing, with a change in the characters of the imprint code.

V. February 29, 2008

1. New strengths of Opana ER, 7.5-mg, 15-mg, and 30-mg, added.

VI. October 4, 2010

1. The package insert was converted into the Physicians Labeling Rule (PLR) format as set forth under 21 CFR 201.56 and 21 CFR 201.57.

VII. July 9, 2012

1. FDA approved ER/LA Opioid Class REMS and standardized the package inserts for all ER/LA opioids.

2. The **Boxed Warning** language was changed almost in its entirety.

2012 Package Insert
<p>WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, ACCIDENTAL EXPOSURE, and INTERACTION WITH ALCOHOL</p> <p><u>Abuse Potential</u> OPANA ER contains oxymorphone, an opioid agonist and Schedule II controlled substance with abuse liability similar to other opioid agonists, legal or illicit [see <i>Warnings and Precautions</i> (5.1)]. A patient's risk for opioid abuse or addiction prior to prescribing OPANA ER. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients on OPANA ER for signs of misuse, abuse, and addiction during treatment [see <i>Drug Abuse and Dependence</i> (9)].</p> <p><u>Life-threatening Respiratory Depression</u> Respiratory depression, including fatal cases, may occur with use of OPANA ER, even when it has been used as recommended and not misused or abused [see <i>Warnings and Precautions</i> (5.2)]. Titration and titration are essential and OPANA ER should only be prescribed by healthcare professionals knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of OPANA ER or following a dose increase. Instruct patients to swallow OPANA ER tablets whole. Crushing, dissolving, or chewing OPANA ER can cause rapid absorption of a potentially fatal dose of oxymorphone.</p> <p><u>Accidental Exposure</u> Accidental ingestion of OPANA ER, especially in children, can result in a fatal overdose of oxymorphone [see <i>Warnings and Precautions</i> (5.3)].</p> <p><u>Interaction with Alcohol</u> The co-ingestion of alcohol with OPANA ER may result in an increase of plasma levels and potential for overdose of oxymorphone [see <i>Warnings and Precautions</i> (5.4)]. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on OPANA ER.</p>

3. The Limitation of Usage language in the **INDICATIONS AND USAGE** section changed.

2012 Package Insert
<p><u>Limitation of Usage:</u> OPANA ER is not intended for use:</p> <ul style="list-style-type: none"> • As an as-needed (prn) analgesic • For pain that is mild or not expected to persist for an extended period of time • For acute pain • For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

4. The entire **DOSAGE AND ADMINISTRATION** section has been reworked but no significant substantive changes were made.

5. A new Section 5.1 Abuse Potential added to **WARNINGS AND PRECAUTIONS** incorporating the former Section 5.3 Misuse, Abuse and Diversion of Opioids, and adding the language below.

2012 Package Insert

“Assess each patient’s risk for opioid abuse or addiction prior to prescribing OPANA ER. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.”

6. Section 5.2 Respiratory Depression in **WARNINGS AND PRECAUTIONS** section was replaced with Section 5.2 Life Threatening Respiratory Depression.

2012 Package Insert

Section 5.2 Life Threatening Respiratory Depression: Respiratory depression is the primary risk of OPANA ER. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a “sighing” pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status [see Overdosage (10)]. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OPANA ER, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with OPANA ER and following dose increases. Instruct patients against use by individuals other than the patient for whom OPANA ER was prescribed and to keep OPANA ER out of the reach of children, as such inappropriate use may result in fatal respiratory depression. To reduce the risk of respiratory depression, proper dosing and titration of OPANA ER are essential [see Dosage and Administration (2.1, 2.2)]. Overestimating the OPANA ER dose when converting patients from another opioid product can result in fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-release opioids when used as recommended and not misused or abused. To

further reduce the risk of respiratory depression, consider the following:

- Proper dosing and titration are essential and OPANA ER should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.
- Instruct patients to swallow OPANA ER tablets intact. The tablets are not to be crushed, dissolved, or chewed. The resulting oxymorphone dose may be fatal, particularly in opioid-naïve individuals.
- OPANA ER is contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression [see Contraindications (4)].

7. New section on accidental exposure added to **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

Section 5.3 Accidental Exposure: “Accidental consumption of OPANA ER, especially in children, can result in a fatal overdose of oxymorphone.”

8. Section 5.4 Interactions with Alcohol and other CNS Depressants in **WARNINGS AND PRECAUTIONS** was replaced with two sections, Section 5.4 Interaction with Alcohol and Section 5.7 Interactions with CNS Depressants and Illicit Drugs. See the new sections below.

2012 Package Insert

5.4 Interaction with Alcohol: The co-ingestion of alcohol with OPANA ER can result in an increase of oxymorphone plasma levels and potentially fatal overdose of oxymorphone. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on OPANA ER therapy [see Clinical Pharmacology (12.3)].

5.7 Interactions with CNS Depressants and Illicit Drugs: Hypotension, profound sedation, coma, or respiratory depression may result if OPANA ER is used concomitantly with other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). When considering the use of OPANA ER in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient’s response, including the degree of tolerance that has developed to CNS depression. Additionally, consider the patient’s use, if any, of alcohol or illicit drugs that cause CNS depression. If OPANA ER therapy is to be initiated in a patient taking a CNS depressant, start with a lower OPANA ER dose than usual and monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant [see Drug Interactions (7.2)].

9. A new Section 5.5 Elderly, Cachectic, and Debilitated Patients was added to the **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

Section 5.5 Elderly, Cachectic, and Debilitated Patients: “Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance compared to younger, healthier patients. Therefore, monitor such patients closely, particularly when initiating and titrating OPANA ER and when OPANA ER is given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.2)].”

10. A new Section 5.13 Avoidance of Withdrawal was added to **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

“Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received or are receiving a course of therapy with an opioid agonist analgesic, including OPANA ER. In these patients, mixed agonists/antagonists analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing OPANA ER, gradually taper the dose [see Dosage and Administration (2.3)]. Do not abruptly discontinue OPANA ER.”

11. New language added to **ADVERSE REACTION/Post-marketing Experience** section.

2012 Package Insert

“*Nervous system disorder:* amnesia, convulsion, memory impairment.”

VIII. April 16, 2014

1. The Abuse Potential section of **Boxed Warning** was renamed Addiction, Abuse, and Misuse and the following language deleted.

2014 Package Insert

“The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder).”

2. New warning of Neonatal Opioid Withdrawal Syndrome added to **Boxed Warning**.

2014 Package Insert
<p>“Neonatal Opioid Withdrawal Syndrome Prolonged use of OPANA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Warnings and Precautions (5.3)].”</p>

3. The indication in **INDICATIONS AND USAGE** section was narrowed.

2014 Package Insert
<p>“OPANA ER is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.”</p> <ul style="list-style-type: none"> • “<u>Limitations on Usage:</u> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OPANA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. OPANA ER is not indicated as an as-needed (prn) analgesic.”

4. New language added to **DOSAGE AND ADMINISTRATION/Initial Dosing** section.

2014 Package Insert
<p>“To avoid medication errors, prescribers and pharmacists must be aware that oxymorphone is available as both immediate-release 5 mg and 10 mg tablets and extended-release 5 mg and 10 mg tablets [see <i>Dosage Forms and Strengths</i>]. OPANA ER should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.”</p>

5. A new subsection added to **DOSAGE AND ADMINISTRATION/Initial Dosing** section.

2014 Package Insert*Use of OPANA ER in Patients who are not Opioid Tolerant*

The starting dose for patients who are not opioid tolerant is OPANA ER 5 mg orally every 12 hours. Patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, ..., 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid. Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.”

6. Changes made to the addiction abuse and misuse language in the **WARNINGS AND PRECAUTIONS** section. (Deleted language is ~~crossed out~~, added language is underlined).

2014 Package Insert**Section 5.1 Addiction, Abuse, and Misuse**

~~“Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit” and replaced with: “As modified-release products such as OPANA ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxymorphone present.”~~

“Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OPANA ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.”

7. A new warning regarding the risk of Neonatal Opioid Withdrawal Syndrome was added to the **WARNINGS AND PRECAUTIONS** section.

2014 Package Insert**“5.3 Neonatal Opioid Withdrawal Syndrome**

Prolonged use of OPANA ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor,

vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.”

IX. December 16, 2016

1. Language regarding risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants added to the **Boxed Warning**.

2016 Package Insert

“Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions 5.5, Drug Interactions (7)]. Reserve concomitant prescribing of OPANA ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.”

2. A new subsection added to **DOSAGE AND ADMINISTRATION** section.

2016 Package Insert

“Subsection 2.1 Important Dosage and Administration Instructions
Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. *[see Warnings and Precautions (5)].”*

3. The language in Subsection 2.4 Discontinuation of OPANA ER in **DOSAGE AND ADMINISTRATION** changed.

2016 Package Insert

“Subsection 2.4 Discontinuation of OPANA ER
When a patient no longer requires therapy with OPANA ER, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OPANA ER *[see Warnings and Precautions (5.13), Drug Abuse and Dependence (9.3)].”*

4. Language describing symptoms of Neonatal Opioid Withdrawal was deleted from **WARNINGS AND PRECAUTIONS/Neonatal Opioid Withdrawal Syndrome** section.

2016 Package Insert

~~“Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.”~~

5. Subsection 5.4 Interactions with Central Nervous System Depressants Risks in **WARNINGS AND PRECAUTIONS** section was replaced with subsection 5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants.

2016 Package Insert

“5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone [see Clinical Pharmacology (12.3)].

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OPANA ER with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Drug Interactions (7)].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients

already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when OPANA ER is used with benzodiazepine or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see *Drug Interactions* (7) and *Patient Counseling Information* (17)].”

6. A new section regarding risk of Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions added to the **WARNINGS AND PRECAUTIONS** section.

2016 Package Insert

“5.6 Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Potentially life-threatening hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients treated with OPANA ER in the postmarket setting. The most commonly described clinical features in these reports were swelling of the face, eyes, mouth, lips, tongue, hands, and/or throat; dyspnea; hives, pruritus, and/or rash; and nausea/vomiting. If anaphylaxis or other hypersensitivity occurs, stop administration of OPANA ER immediately, discontinue OPANA ER permanently, and do not rechallenge with any formulation of oxymorphone. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction [see *Patient Counseling Information* (17)]. “

7. A new section Adrenal Insufficiency added to **RISKS AND PRECAUTIONS** section.

2016 Package Insert

“5.7 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal

insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.”

X. September 19, 2018

1. Information about REMS added to the **Boxed Warning**.

2018 Package Insert
<p><u>Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):</u></p> <p>To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Administration (FDA) has required a REMS for these products <i>[see Warnings and Precautions (5.2)]</i>. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS education programs available to healthcare providers. Healthcare providers are strongly encouraged to:</p> <ul style="list-style-type: none"> • complete a REMS-compliant education program, • counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products, • emphasize to patients and their caregivers the importance of reading the Medication Guide every time they get a refill, and • consider other tools to improve patient, household, and community safety.

2. Information about the REMS added to the **WARNINGS AND PRECAUTIONS** section.

2018 Package Insert
<p>Subsection 5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)</p> <p>To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:</p> <ul style="list-style-type: none"> ▪ Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another

education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.

- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link:
www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities. To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

ENDO
LABEL CHANGES FOR REFORMULATED OPANA ER
(NDA 201655)

SUMMARY OF LABEL CHANGES

- I. December 9, 2011 Initial Label**²⁴
- II. July 9, 2012**²⁵
- FDA approved ER/LA Opioid Class REMS and standardized the package inserts for all ER/LA opioids.
 - The language in **boxed warning** changed
 - The limitation of usage language in the **INDICATION AND USAGE** section changed.
 - The language in **DOSAGE AND ADMINISTRATION** section was redrafted, but no substantive changes were made.
 - New language on abuse potential added to the **WARNINGS AND PRECAUTIONS** section.
 - Warning about respiratory depression in **WARNINGS AND PRECAUTIONS** was replaced with a warning of life threatening respiratory depression.
 - Accidental exposure warning added to the **WARNINGS AND PRECAUTIONS** section.
 - Section 5.4 Interactions with Alcohol and other CNS Depressants in **WARNINGS AND PRECAUTIONS** section was replaced with two sections, Section 5.4 Interaction with Alcohol and Section 5.7 Interactions with CNS Depressants and Illicit Drugs.
 - New section 5.5 Elderly, Cachectic, and Debilitated Patients was added to the **WARNINGS AND PRECAUTIONS** section.
 - A new Section 5.13 Avoidance of Withdrawal was added to **WARNINGS AND PRECAUTIONS** section.
 - New language added to **ADVERSE REACTION/Post-marketing Experience** section.
- III. January 14, 2013**²⁶
- 1. Language regarding the ghost pill phenomenon added to the *Important Administration Instructions* subsection of **PATIENT COUNSELING INFORMATION** section.
- IV. April 16, 2014**²⁷
- 1. The Abuse Potential warning in **Boxed Warnings** was replaced with an Addiction, Abuse, and Misuse warning.

²⁴ EPI000016128.

²⁵ https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/201655s002lbl.pdf

²⁶ EPI000033318.

²⁷ EPI002482861 (approved label); ENDO-OR-CID-01195630 (FDA letter notifying of label change).

2. New warning regarding Neonatal Opioid Withdrawal Syndrome added to the **Boxed Warnings**.
3. The indication in **INDICATIONS AND USAGE** section was narrowed to severe pain for which other treatment options are inadequate.
4. New language added to **DOSAGE AND ADMINISTRATION/Initial Dosing** section.
5. A new subsection added to **DOSAGE AND ADMINISTRATION/Initial Dosing** section.
6. Changes made to the addiction abuse and misuse language in the **WARNINGS AND PRECAUTIONS** section.
7. A new warning regarding the risk of Neonatal Opioid Withdrawal Syndrome was added to the **WARNINGS AND PRECAUTIONS** section.

V. **December 16, 2016**²⁸

- Risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants added to the **Boxed Warning**.
- A new subsection added to **DOSAGE AND ADMINISTRATION** section.
- The language in Subsection 2.4 Discontinuation of OPANA ER in **DOSAGE AND ADMINISTRATION** changed.
- Language describing symptoms of Neonatal Opioid Withdrawal was deleted from **WARNINGS AND PRECAUTIONS/Neonatal Opioid Withdrawal Syndrome** section.
- Subsection 5.4 Interactions with Central Nervous System Depressants Risks in **WARNINGS AND PRECAUTIONS** section was replaced with subsection 5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants.
- A new section regarding risk of Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions added to the **WARNINGS AND PRECAUTIONS** section.
- A new section Adrenal Insufficiency added to **RISKS AND PRECAUTIONS** section.

VI. **September 19, 2018**²⁹

1. Information about REMS added to the **Boxed Warning**.
2. Information about the REMS added to the **WARNINGS AND PRECAUTIONS** section.

²⁸ ENDO-OPIOID_MDL-00046776.

²⁹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/201655s024s0251bl.pdf

DETAILED REVIEW OF LABEL CHANGES

I. December 9, 2011

1. Approved **INDICATIONS AND USAGE**.

Initial Package Insert

OPANA ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

Limitations of Usage

OPANA ER is not intended for use as an as needed analgesic.

OPANA ER is not indicated for pain in the immediate post-operative period if the pain is mild, or not expected to persist for an extended period of time.

OPANA ER is only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate or severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines).

2. Approved **Boxed Warning**

Initial Package Insert

WARNING: POTENTIAL FOR ABUSE, IMPORTANCE OF PROPER PATIENT SELECTION AND LIMITATIONS OF USE

Potential for Abuse

OPANA ER contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. (9)

Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illegal. Physicians should be alert to the possibility of abuse and should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9.2)

Proper Patient Selection

OPANA ER is an extended-release oral formulation of oxymorphone indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

Limitations of Use

OPANA ER is NOT intended for use as an as needed analgesic. (1)

OPANA ER tablets are to be swallowed whole and are not to be cut, broken, chewed or crushed. Taking cut, broken, chewed, dissolved, or crushed OPANA ER tablets lead to rapid release and absorption of a potentially fatal dose of oxymorphone. (2)

Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

II. July 9, 2012

1. FDA approved ER/LA Opioid Class REMS and standardized the package inserts for all ER/LA opioids.
2. The **Boxed Warning** language was changed almost in its entirety.

2012 Package Insert

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, ACCIDENTAL EXPOSURE, and INTERACTION WITH ALCOHOL

Abuse Potential

OPANA ER contains oxymorphone, an opioid agonist and Schedule II controlled substance with abuse liability similar to other opioid agonists, legal or illicit [see Warnings and Precautions (5.1)]. Assess a patient's risk for opioid abuse or addiction prior to prescribing OPANA ER. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients on OPANA ER for signs of misuse, abuse, and addiction during treatment [see Drug Abuse and Dependence (9)].

Life-threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of OPANA ER, even when it has been used as recommended and not misused or abused [see Warnings and Precautions (5.2)]. Titration and monitoring are essential and OPANA ER should only be prescribed by healthcare professionals knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of OPANA ER or following a dose increase. Instruct patients to swallow OPANA ER tablets whole. Crushing, dissolving, or chewing OPANA ER can cause rapid release and absorption of a potentially fatal dose of oxymorphone.

Accidental Exposure

Accidental ingestion of OPANA ER, especially in children, can result in a fatal overdose of oxymorphone [see Warnings and Precautions (5.3)].

Interaction with Alcohol

The co-ingestion of alcohol with OPANA ER may result in an increase of plasma levels and potential for overdose of oxymorphone [see Warnings and Precautions (5.4)]. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on OPANA ER.

3. The Limitation of Usage language in the **INDICATIONS AND USAGE** section changed.

2012 Package Insert

Limitation of Usage: OPANA ER is not intended for use:

- As an as-needed (prn) analgesic
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

4. The entire **DOSAGE AND ADMINISTRATION** section has been reworked but no significant substantive changes were made.
5. A new Section 5.1 Abuse Potential added to **WARNINGS AND PRECAUTIONS** incorporating the former Section 5.3 Misuse, Abuse and Diversion of Opioids, and adding the language below.

2012 Package Insert

“Assess each patient’s risk for opioid abuse or addiction prior to prescribing OPANA ER. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.”

6. Section 5.2 Respiratory Depression in **WARNINGS AND PRECAUTIONS** section was replaced with Section 5.2 Life Threatening Respiratory Depression.

2012 Package Insert

Section 5.2 Life Threatening Respiratory Depression: Respiratory depression is the primary risk of OPANA ER. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a “sighing” pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status [see Overdosage (10)]. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OPANA ER, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with OPANA ER and following dose increases. Instruct patients against use by individuals other than the patient for whom OPANA ER was prescribed and to keep OPANA ER out of the reach of children, as such inappropriate use may result in fatal respiratory depression. To reduce the risk of respiratory depression, proper dosing and titration of OPANA ER are essential [see Dosage and Administration (2.1,

2.2)]. Overestimating the OPANA ER dose when converting patients from another opioid product can result in fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-release opioids when used as recommended and not misused or abused. To further reduce the risk of respiratory depression, consider the following:

- Proper dosing and titration are essential and OPANA ER should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.
- Instruct patients to swallow OPANA ER tablets intact. The tablets are not to be crushed, dissolved, or chewed. The resulting oxymorphone dose may be fatal, particularly in opioid-naïve individuals.
- OPANA ER is contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression [see Contraindications (4)].

7. New section on accidental exposure added to **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

Section 5.3 Accidental Exposure: “Accidental consumption of OPANA ER, especially in children, can result in a fatal overdose of oxymorphone.”

8. Section 5.4 Interactions with Alcohol and other CNS Depressants in **WARNINGS AND PRECAUTIONS** was replaced with two sections, Section 5.4 Interaction with Alcohol and Section 5.7 Interactions with CNS Depressants and Illicit Drugs. See the new sections below.

2012 Package Insert

5.4 Interaction with Alcohol: The co-ingestion of alcohol with OPANA ER can result in an increase of oxymorphone plasma levels and potentially fatal overdose of oxymorphone. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on OPANA ER therapy [see Clinical Pharmacology (12.3)].

5.7 Interactions with CNS Depressants and Illicit Drugs: Hypotension, profound sedation, coma, or respiratory depression may result if OPANA ER is used concomitantly with other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). When considering the use of OPANA ER in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient’s response, including the degree of tolerance that has developed to CNS depression. Additionally, consider the patient’s use, if any, of alcohol or illicit drugs that cause CNS depression. If OPANA ER therapy is to be initiated in a

patient taking a CNS depressant, start with a lower OPANA ER dose than usual and monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant [see Drug Interactions (7.2)].

9. A new Section 5.5 Elderly, Cachectic, and Debilitated Patients was added to the **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

Section 5.5 Elderly, Cachectic, and Debilitated Patients: “Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance compared to younger, healthier patients. Therefore, monitor such patients closely, particularly when initiating and titrating OPANA ER and when OPANA ER is given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.2)].”

10. A new Section 5.13 Avoidance of Withdrawal was added to **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

“Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received or are receiving a course of therapy with an opioid agonist analgesic, including OPANA ER. In these patients, mixed agonists/antagonists analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing OPANA ER, gradually taper the dose [see Dosage and Administration (2.3)]. Do not abruptly discontinue OPANA ER.”

11. New language added to **ADVERSE REACTION/Post-marketing Experience** section.

2012 Package Insert

“Nervous system disorder: amnesia, convulsion, memory impairment.”

III. January 14, 2013

1. Language regarding the ghost pill phenomenon added to the *Important Administration Instructions* subsection of **PATIENT COUNSELING INFORMATION** section.

2013 Package Insert

“Occasionally, the inactive ingredients of OPANA ER may be eliminated as a soft mass in the stool that may resemble the original tablet. Patients should be informed that the active medication has already been absorbed by the time the patient sees the soft mass.”

IV. April 16, 2014

1. The Abuse Potential section of **Boxed Warning** was renamed Addiction, Abuse, and Misuse and the following language deleted.

2014 Package Insert

“The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder).”

2. New warning of Neonatal Opioid Withdrawal Syndrome added to **Boxed Warning**.

2014 Package Insert

“Neonatal Opioid Withdrawal Syndrome Prolonged use of OPANA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Warnings and Precautions (5.3)].”

3. The indication in **INDICATIONS AND USAGE** section was narrowed.

2014 Package Insert

“OPANA ER is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.”

- **“Limitations on Usage: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OPANA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. OPANA ER is not indicated as an as-needed (prn) analgesic.”**

4. New language added to **DOSAGE AND ADMINISTRATION/Initial Dosing** section.

2014 Package Insert

“To avoid medication errors, prescribers and pharmacists must be aware that oxymorphone is available as both immediate-release 5 mg and 10 mg tablets and extended-release 5 mg and 10 mg tablets [*see Dosage Forms and Strengths*]. OPANA ER should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.”

5. A new subsection added to **DOSAGE AND ADMINISTRATION/Initial Dosing** section.

2014 Package Insert

Use of OPANA ER in Patients who are not Opioid Tolerant

The starting dose for patients who are not opioid tolerant is OPANA ER 5 mg orally every 12 hours. Patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, ..., 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid. Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.”

6. Changes made to the addiction abuse and misuse language in the **WARNINGS AND PRECAUTIONS** section. (Deleted language is ~~crossed out~~, added language is underlined).

2014 Package Insert

Section 5.1 Addiction, Abuse, and Misuse

~~“Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit” and replaced with: “As modified-release products such as OPANA ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxymorphone present.”~~

“Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OPANA ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.”

7. A new warning regarding the risk of Neonatal Opioid Withdrawal Syndrome was added to the **WARNINGS AND PRECAUTIONS** section.

2014 Package Insert**“5.3 Neonatal Opioid Withdrawal Syndrome**

Prolonged use of OPANA ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.”

V. December 16, 2016

1. Language regarding risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants added to the **Boxed Warning**.

2016 Package Insert

“Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions 5.5, Drug Interactions (7)]. Reserve concomitant prescribing of OPANA ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.”

2. A new subsection added to **DOSAGE AND ADMINISTRATION** section.

2016 Package Insert

“Subsection 2.1 Important Dosage and Administration Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. *[see Warnings and Precautions (5)].*”

3. The language in Subsection 2.4 Discontinuation of OPANA ER in **DOSAGE AND ADMINISTRATION** changed.

2016 Package Insert

“Subsection 2.4 Discontinuation of OPANA ER

When a patient no longer requires therapy with OPANA ER, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OPANA ER *[see Warnings and Precautions (5.13), Drug Abuse and Dependence (9.3)].*”

4. Language describing symptoms of Neonatal Opioid Withdrawal was deleted from **WARNINGS AND PRECAUTIONS/Neonatal Opioid Withdrawal Syndrome** section.

2016 Package Insert

~~“Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.”~~

5. Subsection 5.4 Interactions with Central Nervous System Depressants Risks in **WARNINGS AND PRECAUTIONS** section was replaced with subsection 5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants.

2016 Package Insert

“5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Patients must not consume alcoholic beverages or prescription or non-

prescription products containing alcohol while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone [see Clinical Pharmacology (12.3)].

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OPANA ER with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Drug Interactions (7)].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when OPANA ER is used with benzodiazepine or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see Drug Interactions (7) and Patient Counseling Information (17)].”

6. A new section regarding risk of Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions added to the **WARNINGS AND PRECAUTIONS** section.

2016 Package Insert**“5.6 Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions**

Potentially life-threatening hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients treated with OPANA ER in the postmarket setting. The most commonly described clinical features in these reports were swelling of the face, eyes, mouth, lips, tongue, hands, and/or throat; dyspnea; hives, pruritus, and/or rash; and nausea/vomiting. If anaphylaxis or other hypersensitivity occurs, stop administration of OPANA ER immediately, discontinue OPANA ER permanently, and do not rechallenge with any formulation of oxymorphone. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction [see Patient Counseling Information (17)]. “

7. A new section Adrenal Insufficiency added to **RISKS AND PRECAUTIONS** section.

2016 Package Insert**“5.7 Adrenal Insufficiency**

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.”

VI. September 19, 2018

1. Information about REMS added to the **Boxed Warning**.

2018 Package Insert
<p><u>Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):</u></p> <p>To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, Administration (FDA) has required a REMS for these products <i>[see Warnings and Precautions (5.2)</i> requirements of the REMS, drug companies with approved opioid analgesic products must make REMS education programs available to healthcare providers. Healthcare providers are strongly encouraged to:</p> <ul style="list-style-type: none"> • complete a REMS-compliant education program, • counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage of these products, • emphasize to patients and their caregivers the importance of reading the Medication Guide every time provided by their pharmacist, and • consider other tools to improve patient, household, and community safety.

2. Information about the REMS added to the **WARNINGS AND PRECAUTIONS** section.

2018 Package Insert
<p>Subsection 5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)</p> <p>To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:</p> <ul style="list-style-type: none"> ▪ Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain. ▪ Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG. ▪ Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.

- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities. To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

VII. April 16, 2014

1. **OVERVIEW:** FDA-required, class-wide labeling changes to reflect new safety information

VIII. September 19, 2018

1. **OVERVIEW:** Information about REMS added to the label.
2. **Boxed Warning:**
 1. The **Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)** added to the **Boxed Warning**.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.2)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

3. WARNINGS AND PRECAUTIONS

1. REMS were also added to **Warnings and Precautions** as **Subsection 5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**:

- To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:
 - Complete a REMS-compliant education program offered by an accredited provider of continuing

education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.

- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them. Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities. To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

JANSSEN
LABEL CHANGES FOR DURAGESIC
NDA #19-813

SUMMARY OF LABEL CHANGES

- XI. August 1990**³⁰
1. Initial label.
- XII. January 1994**³¹
1. The language in **INDICATIONS** changed.
2. A **Boxed Warning** was added.
- XIII. April 1998**³²
1. A section on **Pediatrics** was added to **WARNINGS** and **PRECAUTIONS**.
2. **CONTRAINDICATIONS** updated
- XIV. May 20, 2003**³³
1. New **indication** added to include children over 2 years.
2. Language was added to **Boxed Warning**.
3. Language was added to **DRUG ABUSE AND ADDICTION** section.
- XV. February 4, 2005**³⁴
1. The language in label **INDICATIONS** changed.
2. The language in **WARNINGS AND PRECAUTIONS** was changed.
3. **New language added in form of ABUSE, MISUSE AND DIVERSION section.**
4. New language in **DRUG ABUSE AND ADDICTION** was added.
5. New language added in form of **SPECIAL PRECAUTIONS** section.
- XVI. July 31, 2009**³⁵
▪ Format of **SPECIAL PRECAUTIONS** section changed, but not substantive changes.
▪ Pharmacokinetics changed.
- XVII. July 9, 2012**³⁶
1. New language was added to **INDICATIONS** specifying “opioid-tolerant”.
2. A new section on **ABUSE POTENTIAL** was added.

³⁰ JAN-MS-00238727

³¹ JAN-MS-02133850

³² JAN-MS-00907134; JAN-MS-02133850.

³³ FDA Letter, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2003/19813se1-036ltr.pdf (last visited March 25, 2019); FDA Label, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/19813se1-036_duragesic_lbl.pdf (last visited March 25, 2019)

³⁴ FDA Label, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/19813s039lbl.pdf (last visited March 25, 2019)

³⁵ FDA Label, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019813s044lblnew.pdf (last visited March 25, 2019)

³⁶ FDA Label, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019813s052lbl.pdf (last visited March 25, 2019)

3. Language describing the potential interactions other medications, other drugs and alcohol was added to **WARNINGS AND PRECAUTIONS**.
4. Formatting change to patient insert.

XVIII. April 16, 2014³⁷

- Language for use in children over 2 years removed from **INDICATIONS**.
- New subsection added under **WARNINGS AND PRECAUTIONS** for **LIMITATIONS OF USE**.

XIX. December 16, 2016³⁸

1. New language added to **Boxed Warning** about concomitant use of benzodiazepines or other CNS depressants.
2. New language added to **Limitations of Use** subheading under **INDICATIONS** to include “not suitable as PRN.”

³⁷ FDA Label, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019813s063lbl.pdf (last visited March 25, 2019)

³⁸ FDA Label, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019813s069lbl.pdf (last visited March 25, 2019)

DETAILED REVIEW OF LABEL CHANGES

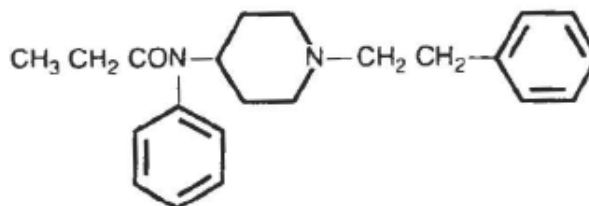
I. August 1990 Initial Label

▪ APPROVED DESCRIPTION

August 1990 Package Insert

DESCRIPTION

DURAGESIC is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. The chemical name is N-phenyl-N-(1-2-phenylethyl-4-piperidyl) propanamide. The structural formula is



▪ APPROVED INDICATION AND USAGE.

August 1990 Package Insert

DURAGESIC is indicated in the management of chronic pain in patients requiring opioid analgesia.

DURAGESIC is not recommended in the management of postoperative pain because it has not been adequately studied in these patients and because of the interpatient variability in absorption and disposition of fentanyl seen in the controlled clinical trials. Based on the information available, it is not possible to identify factors to be used to select a dose which will be safe and effective in individual postoperative patients.

In patients with chronic pain, it is possible to individually titrate the dose of the transdermal system to minimize the risk of adverse effects while providing analgesia. For the majority of the patients DURAGESIC is a safe and effective alternative to other opioid regimens (see DOSAGE AND ADMINISTRATION).

▪ Approved WARNINGS.

- There is also a warning on the exterior packaging (illustrated above) stating: "WARNING: May be habit forming."

August 1990 Package Insert

WARNINGS
 PATIENTS WHO HAVE EXPERIENCED ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 12 HOURS AFTER DURAGESIC REMOVAL SINCE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND REACH AN APPROXIMATE 50% REDUCTION IN SERUM CONCENTRATIONS 17 HOURS AFTER SYSTEM REMOVAL.
 DURAGESIC SHOULD BE PRESCRIBED ONLY BY PERSONS KNOWLEDGEABLE IN THE CONTINUOUS ADMINISTRATION OF POTENT OPIOIDS, IN THE MANAGEMENT OF PATIENTS RECEIVING POTENT OPIOIDS FOR TREATMENT OF PAIN, AND IN THE DETECTION AND MANAGEMENT OF HYPOVENTILATION INCLUDING THE USE OF OPIOID ANTAGONISTS.
 THE CONCOMITANT USE OF OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS, INCLUDING OTHER OPIOIDS, SEDATIVES OR HYPNOTICS, GENERAL ANESTHETICS, PHENOTHIAZINES, TRANQUILIZERS, SKELETAL MUSCLE RELAXANTS, SEDATING ANTI-HISTAMINES, AND ALCOHOLIC BEVERAGES MAY PRODUCE ADDITIVE DEPRESSANT EFFECTS. HYPOVENTILATION, HYPOTENSION AND PROFOUND SEDATION OR COMA MAY OCCUR. WHEN SUCH COMBINED THERAPY IS CONTEMPLATED, THE DOSE OF ONE OR BOTH AGENTS SHOULD BE REDUCED BY AT LEAST 50%.
PRECAUTIONS

August 1990 Drug of Alcohol Dependence

Use of DURAGESIC in combination with alcoholic beverages and/or other CNS depressants can result in increased risk to the patient. DURAGESIC should be used with caution in individuals who have a history of drug or alcohol abuse, especially if they are outside a medically controlled environment.

August 1990 DRUG ABUSE AND DEPENDENCE

Fentanyl is a Schedule II controlled substance and can produce drug dependence similar to that produced by morphine. DURAGESIC therefore has the potential for abuse. Tolerance, physical, and psychological dependence may develop upon repeated administration of opioids, iatrogenic addiction following opioid administration is relatively rare. Physicians should not let concerns of physical dependence deter them from using adequate amounts of opioids in the management of severe pain when such use is indicated.

August 1990 PRECAUTIONS

PRECAUTIONS

General

DURAGESIC doses greater than 25 µg/h are too high for initiation of therapy in non opioid-tolerant patients and should not be used to begin DURAGESIC therapy in these patients.

DURAGESIC may impair mental and/or physical ability required for the performance of potential hazardous tasks (eg driving, operating machinery). Patients who have been given DURAGESIC should not drive or operate dangerous machinery unless they are tolerant to the side effects of the drug.

Patients should be instructed to keep both used and unused systems out of the reach of children. Used systems should be folded so that the adhesive side of the system adheres to itself and flushed down the toilet immediately upon removal. Patients should be advised to dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused system should be removed from their pouch and flushed down the toilet.

II. January 1994

1. Additional language added to **INDICATION** about lesser means of treatment such as acetaminophen-opioid combinations, NSAIDs or PRN dosing.

January 1994 Package Insert

DURAGESIC is indicated in the management of chronic pain in patients who require continuous opioid analgesia **for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids.**

2. **January 1994 Boxed Warning.**

1994 Boxed Warning

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC IS CONTRAINDICATED:

- In the management of acute or post-operative pain, including use in out-patient surgeries
- In the management of mild or intermittent pain responsive to PRN or non-opioid therapy
- In doses exceeding 25 mcg/hour at the initiation of opioid therapy

(See CONTRAINDICATIONS for further information.)

DURAGESIC SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING. (See PRECAUTIONS - Pediatric Use.)

DURAGESIC is indicated for treatment of chronic pain (such as that of malignancy) that:

- cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids and
- requires continuous opioid administration.

The 50, 75, and 100 mcg/hour dosages should **ONLY** be used in patients who are already on and are tolerant to opioid therapy.

III. April 1998

1. **WARNINGS** revised to include that Duragesic should not be administered to children

1998 Package Insert

WARNINGS

DURAGESIC® SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING. (See PRECAUTIONS-Pediatric Use.)

2. **CONTRAINDICATIONS** updated to include acute/post-operative pain, mild pain, and in doses exceeding 25 ug/hr at initiation of opioid therapy.

1998 Package Insert

CONTRAINDICATIONS

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC® IS CONTRAINDICATED:

- in the management of acute or post-operative pain, including use in out-patient surgeries because there is no opportunity for proper dose titration (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION),
- in the management of mild or intermittent pain that can otherwise be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids, and
- in doses exceeding 25 µg/h at the initiation of opioid therapy because of the need to individualize dosing by titrating to the desired analgesic effect.

IV. May 20, 2003

1. New language added to include children over 2 years in **WARNINGS**.

2003 Package Insert

DURAGESIC® (fentanyl transdermal system) is indicated in the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids.

New indication: “This supplemental new drug application provides for use of Duragesic® (Fentanyl Transdermal System) in pediatric patients 2 years of age and older.”

2003 Package Insert

Pediatrics

The safety of DURAGESIC® was evaluated in three open-label trials in 291 pediatric patients, 2 years through 18 years of age, with chronic pain. Starting doses of 25µg/h and higher were used by 181 patients. Approximately 90% of the total daily opioid requirement (DURAGESIC® plus rescue medication) was provided by DURAGESIC®.

2. Language regarding dosing and pediatric use was added to **Boxed Warning**.

2003 Box Warning

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC® (FENTANYL TRANSDERMAL SYSTEM) IS CONTRAINDICATED:

- In the management of acute or post-operative pain, including use in out-patient surgeries
 - In the management of mild or intermittent pain responsive to PRN or non-opioid therapy
 - In doses exceeding 25 µg/h at the initiation of opioid therapy
- (See CONTRAINDICATIONS for further information.)

SAFETY OF DURAGESIC® HAS NOT BEEN ESTABLISHED IN CHILDREN UNDER 2 YEARS OF AGE. DURAGESIC® SHOULD BE ADMINISTERED TO CHILDREN ONLY IF THEY ARE OPIOID-TOLERANT AND AGE 2 YEARS OR OLDER (See PRECAUTIONS - Pediatric Use.)

DURAGESIC® is indicated for treatment of chronic pain (such as that of malignancy) that:

- Cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids and
- Requires continuous opioid administration.

The 50, 75, and 100 µg/h dosages should ONLY be used in patients who are already on and are tolerant to opioid therapy.

3. Language was added to **DRUG ABUSE AND DEPENDENCE** about patients informing doctors if they have a history of drug or alcohol abuse.

2003 Package Insert

Before using DURAGESIC®, tell your health care provider if you:...Have a history of drug or alcohol abuse

PREVENT THEFT AND MISUSE. DURAGESIC® CONTAINS A NARCOTIC PAIN MEDICINE THAT CAN BE A TARGET FOR PEOPLE WHO ABUSE PRESCRIPTION MEDICINES. KEEP YOUR DURAGESIC® IN A SAFE PLACE, TO PROTECT IT FROM THEFT. NEVER GIVE DURAGESIC® TO ANYONE ELSE BECAUSE IT MAY BE DANGEROUS TO THEM. SELLING OR GIVING AWAY THIS MEDICINE IS AGAINST THE LAW.

V. February 4, 2005

1. Almost entire **Boxed Warning** changed including of “FOR USE IN OPIOID-TOLERANT PATIENTS ONLY”

Full Prescribing Information

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

DURAGESIC® contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that:

- requires continuous, around-the-clock opioid administration for an extended period of time, and
- cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

DURAGESIC® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC® 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.

Because serious or life-threatening hypoventilation could occur, DURAGESIC® (fentanyl transdermal system) is contraindicated:

- in patients who are not opioid-tolerant
- in the management of acute pain or in patients who require opioid analgesia for a short period of time
- in the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- in the management of mild pain
- in the management of intermittent pain [e.g., use on an as needed basis (prn)]

(See CONTRAINDICATIONS for further information.)

Since the peak fentanyl levels occur between 24 and 72 hours of treatment, prescribers should be aware that serious or life threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period.

The concomitant use of DURAGESIC® with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving DURAGESIC® and potent CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted. (See CLINICAL PHARMACOLOGY – Drug Interactions, WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION for further information.)

The safety of DURAGESIC® has not been established in children under 2 years of age. DURAGESIC® should be administered to children only if they are opioid-tolerant and 2 years of age or older (see PRECAUTIONS - Pediatric Use).

DURAGESIC® is ONLY for use in patients who are already tolerant to opioid therapy of comparable potency. Use in non-opioid tolerant patients may lead to fatal respiratory depression. Overestimating the DURAGESIC® dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 17 hours of DURAGESIC®, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours.

DURAGESIC® can be abused in a manner similar to other opioid agonists, legal or illicit. This risk should be considered when administering, prescribing, or dispensing DURAGESIC® in situations where the healthcare professional is concerned about increased risk of misuse, abuse or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

DURAGESIC® patches are intended for transdermal use (on intact skin) only. Using damaged or cut DURAGESIC® patches can lead to the rapid release of the contents of the DURAGESIC® patch and absorption of a potentially fatal dose of fentanyl.

2. Addition of “persistent” to **INDICATION**.

2005 Package Insert

INDICATIONS AND USAGE

DURAGESIC® is indicated for management of persistent, moderate to severe chronic pain that:

- requires continuous, around-the-clock opioid administration for an extended period of time, and
- cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids

2005 Full Prescribing Information

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Patients receiving opioids should be routinely monitored for signs of misuse, abuse, and addiction. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction.

3. The language in **WARNINGS AND PRECAUTIONS** was changed.

2005 Box Warning

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC® (FENTANYL TRANSDERMAL SYSTEM) IS CONTRAINDICATED:

- In the management of acute or post-operative pain, including use in out-patient surgeries
- In the management of mild or intermittent pain responsive to PRN or non-opioid therapy
- In doses exceeding 25 µg/h at the initiation of opioid therapy

(See CONTRAINDICATIONS for further information.)

SAFETY OF DURAGESIC® HAS NOT BEEN ESTABLISHED IN CHILDREN UNDER 2 YEARS OF AGE. DURAGESIC® SHOULD BE ADMINISTERED TO CHILDREN ONLY IF THEY ARE OPIOID-TOLERANT AND AGE 2 YEARS OR OLDER (See PRECAUTIONS - Pediatric Use.)

DURAGESIC® is indicated for treatment of chronic pain (such as that of malignancy) that:

- Cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids and
- Requires continuous opioid administration.

The 50, 75, and 100 µg/h dosages should **ONLY** be used in patients who are already on and are tolerant to opioid therapy.

4. New language in **MISUSE, ABUSE AND DIVERSION** was added.

2005 Full Prescribing Information

Misuse, Abuse and Diversion of Opioids

Fentanyl is an opioid agonist of the morphine-type. Such drugs are sought by abusers and people with addiction disorders and are subject to criminal diversion.

Fentanyl can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing DURAGESIC® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

DURAGESIC® has been reported as being abused by other methods and routes of administration. These practices will result in uncontrolled delivery of the opioid, posing a significant risk to the abuser that could result in overdose and death (see WARNINGS and DRUG ABUSE AND ADDICTION).

2005 Full Prescribing Information

Concerns about abuse, addiction and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic product carries the risk of addiction even under appropriate medical use.

Healthcare professionals should contact their state professional licensing board or controlled substances authority for information on how to prevent and detect a diversion of this product.

5. New language added in form of **DRUG ABUSE AND ADDICTION** section defining addiction and describing potential indicators of addiction.

2005 Full Prescribing Information

The high content of fentanyl in the patches (DURAGESIC®) may be a particular concern for abuse and diversion.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

“Drug seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to accept appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may be accompanied by concurrent

2005 Full Prescribing Information

and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, diversion, or in combination with other psychoactive substances. Since DURAGESIC® is a potent Schedule II opioid, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that should be taken to prevent abuse of opioid drugs.

DURAGESIC® patches are intended for transdermal use (to be applied to intact skin). Using cut or damaged DURAGESIC® patches or its contents can lead to release and absorption of a potentially fatal dose of fentanyl.

6. New language about abuse and diversion added to **SPECIAL PRECAUTIONS** section.

2005 Package Insert

Special Precautions

DURAGESIC® contains a high concentration of a potent Schedule II opioid, fentanyl. Schedule II opioid substances which include fentanyl, hydrocodone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression.

2005 Package Insert

can be abused and is subject to criminal diversion. The high concentration of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

VI. July 31, 2009

1. Additions were made in **SPECIAL PRECAUTIONS** section regarding theft and abuse.

2009 Full Prescribing Information

DURAGESIC® contains a high concentration of a potent Schedule II opioid agonist, fentanyl. Schedule II opioid substances which include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches (DURAGESIC®) may be a particular target for abuse and diversion.

DURAGESIC® is a federally controlled substance (C-II) because it can be abused. Keep DURAGESIC® in a safe place to prevent theft. Selling or giving away DURAGESIC® may harm others, and is against the law. • Tell your doctor if you (or a family member) have ever abused or been dependent on alcohol, prescription medicines or street drugs.

2. The Pharmacokinetics section was changed to reflect new drug-in-adhesive matrix designed formulation

2009 Full Prescribing Information

Pharmacokinetics

(see graph and tables)

The DURAGESIC® (fentanyl transdermal system) is a drug-in-adhesive matrix designed formulation. Fentanyl is released from the matrix at a nearly constant amount per unit time. The concentration gradient existing between the matrix and the lower concentration in the skin drives drug release. Fentanyl moves in the direction of the lower concentration at a rate determined by the matrix and the diffusion of fentanyl through the skin layers. While the actual rate of fentanyl delivery to the skin varies over the 72-hour application period, each system is labeled with a nominal flux which represents the average amount of drug delivered to the systemic circulation per hour across average skin.

VII. July 9, 2012

1. New language was added to **INDICATIONS** specifying “opioid-tolerant”.

2012 Full Prescribing Information
DURAGESIC is a transdermal formulation of fentanyl indicated for the management of persistent, moderate to severe chronic pain in opioid-tolerant patients 2 years of age and older when a continuous, around-the-clock opioid analgesic is required for an extended period of time, and the patient cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.

2. A new subsection on **Abuse Potential** was added to **WARNINGS AND PRECAUTIONS**

2012 Full Prescribing information
<p>5.1 Abuse Potential</p> <p>DURAGESIC contains fentanyl, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics. Schedule II opioid substances which include hydromorphone, morphine, oxycodone, fentanyl, oxymorphone and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression. DURAGESIC can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when administering, prescribing, or dispensing DURAGESIC in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion [see <i>Drug Abuse and Dependence (9)</i>].</p> <p>Assess patients for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Routinely monitor all patients receiving opioids for signs of misuse, abuse and addiction since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.</p> <p>Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.</p>

3. Language describing the potential interactions other medications, other drugs and alcohol was added to **WARNINGS AND PRECAUTIONS**.

2012 Full Prescribing Information

5.7 Interactions with Other CNS Depressants, Alcohol, and Drugs of Abuse

The concomitant use of DURAGESIC with other central nervous system depressants, including, but not limited to, other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol, may cause respiratory depression, hypotension, and profound sedation or coma. Monitor patients prescribed concomitant CNS active drugs for signs of sedation and respiratory depression, particularly when initiating therapy with DURAGESIC, and reduce the dose of one or both agents [see *Warnings and Precautions* (5.2)].

VIII. April 16, 2014

1. Language for use in children over 2 years removed from **INDICATIONS**.

2014 Package Insert

DURAGESIC is indicated for the management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

DURAGESIC is a transdermal formulation of fentanyl indicated for the management of persistent, moderate to severe chronic pain in opioid-tolerant patients ~~2-years-of-age-and-older~~ when a continuous, around-the-clock opioid analgesic is required for an extended period of time, and the patient cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.

2. New subsection added under **WARNINGS AND PRECAUTIONS** for **LIMITATIONS OF USE**.

2014 Package Insert

Limitations of use:

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve DURAGESIC for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)

IX. December 16, 2016

1. New language added to **Boxed Warning** about concomitant use of benzodiazepines or other CNS depressants.

2016 Boxed Warning

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; RISK OF INCREASED FENTANYL ABSORPTION WITH APPLICATION OF EXTERNAL HEAT; and RISKS FROM CONCOMITANT USE OF BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
See full prescribing information for complete boxed warning.

- DURAGESIC exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and monitor regularly for these behaviors or conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)
- Accidental exposure to DURAGESIC, especially in children, can result in fatal overdose of fentanyl. (5.3)
- Prolonged use of DURAGESIC during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)
- Concomitant use with CYP 3A4 inhibitors (or discontinuation of CYP 3A4 inducers) can result in a fatal overdose of fentanyl. (5.5)
- Exposure of the DURAGESIC application site and surrounding area to direct external heat sources has resulted in fatal overdose of fentanyl. Warn patients to avoid exposing the DURAGESIC application site and surrounding area to direct external heat sources. (5.6)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.7, 7)

2. New language added to **Limitations of Use** subheading under **INDICATIONS** stating “Not indicated as an as-needed (prn) analgesic.

2016 Package Insert	
	<p><u>Limitations of use:</u></p> <ul style="list-style-type: none">• Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve DURAGESIC for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)• DURAGESIC is not indicated as an as-needed (prn) analgesic

JANSSEN
LABEL CHANGES FOR NUCYNTA IR
(NDA 022304)

SUMMARY OF LABEL CHANGES

- I. November 20, 2008 Initial Label**³⁹
- II. March 2009 Label**⁴⁰
1. New language added to the **INDICATIONS AND USAGE**
- III. July 2013 Label**⁴¹
1. Additional warnings added to the **WARNINGS AND PRECAUTIONS** regarding misuse, abuse, diversion, hypotensive effect, withdrawal, and impaired mental/physical abilities. Revisions also made warnings regarding respiratory depression, interaction with CNS depressants, and patients with intracranial pressure.
- IV. December 2016 Label**⁴²
1. New language added to the **INDICATIONS AND USAGE** regarding severity of pain required and “Limitations of Use” section added.
 2. Warnings for addiction, abuse, and misuse, respiratory depression, accidental neonatal opioid withdrawal syndrome, and risks from concomitant CNS depressant added to **boxed warning**. Addiction and CNS warnings removed from **WARNINGS AND PRECAUTIONS**
- V. September 2018 Label**⁴³
1. Revisions made to **boxed warning** to note that the FDA has required a REMS for the product.

³⁹ Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_Lbl.pdf (last visited March 21, 2009)

⁴⁰ JAN-MS-01249732

⁴¹ JAN-MS-01229368

⁴² Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022304s016lbl.pdf (last visited March 21, 2009)

⁴³ Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022304s019s021lbl.pdf (last visited March 21, 2009)

DETAILED REVIEW OF LABEL CHANGES

I. November 20, 2008 Initial Label

1. Approved **INDICATION AND USAGE**.

2008 Package Insert

[NUCYNTA] is indicated for the relief of moderate to severe acute pain in patients 18 years of age or older.

2. Approved **WARNINGS AND PRECAUTIONS**.

2008 Package Insert

-----WARNINGS AND PRECAUTIONS-----

- Respiratory depression: Increased risk in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction. (5.1)
- CNS effects: Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.2)
- Elevation of intracranial pressure: May be markedly exaggerated in the presence of head injury, other intracranial lesions. (5.3)
- Abuse potential may occur. Monitor patients closely for signs of abuse and addiction. (5.4)
- Impaired mental/physical abilities: Caution must be used with potentially hazardous activities. (5.5)
- Seizures: Use with caution in patients with a history of seizures. (5.7)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic administration. (5.8)

II. March 2009 Label

1. New language noting Nucynta is an opioid analgesic added to the **INDICATIONS AND USAGE**

2009 Package Insert

NUCYNTA is an opioid analgesic indicated for the relief of moderate to severe acute pain in patients 18 years of age or older.

III. July 2013 label

1. Additional warnings added to the **WARNINGS AND PRECAUTIONS** regarding misuse, abuse, diversion, hypotensive effect, withdrawal, and impaired mental/physical abilities. Revisions also made warnings regarding respiratory depression, interaction with CNS depressants, and patients with intracranial pressure

2013 Package Insert

-----WARNINGS AND PRECAUTIONS-----

- Misuse, Abuse and Diversion: NUCYNTA[®] is a Schedule II controlled substance with abuse liability similar to other opioids: monitor patients closely for signs of misuse, abuse and addiction. (5.1)
- Elderly, cachectic, and debilitated patients and patients with chronic pulmonary disease: Monitor closely because of increased risk of respiratory depression. (5.5)
- Interaction with CNS depressants including other opioids, sedatives, alcohol, and illicit drugs: Consider dose reduction of one or both drugs because of additive effects. (5.7)
- Hypotensive effect: Monitor for signs of hypotension.(5.8)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of NUCYNTA[®] in patients

IV. December 2016 Label

1. New language added to the **INDICATIONS AND USAGE** regarding severity of pain required and “Limitations of Use” due to risks of addiction, abuse, and misuse, section added .

2016 Boxed Warning

-----INDICATIONS AND USAGE-----

NUCYNTA tablets are an opioid analgesic indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve NUCYNTA tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products):

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

2. Warnings for addiction, abuse, and misuse, respiratory depression, accidental neonatal opioid withdrawal syndrome, and risks from concomitant CNS depressant added to **boxed warning**. Addiction and CNS warnings removed from **WARNINGS AND PRECAUTIONS**

2016 Boxed Warning

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- NUCYNTA tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)
- Accidental ingestion of NUCYNTA tablets, especially by children, can result in a fatal overdose of tapentadol. (5.2)
- Prolonged use of NUCYNTA tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation (5.4), (7).

2016 Package Insert**-----WARNINGS AND PRECAUTIONS-----**

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.5)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue NUCYNTA tablets if serotonin syndrome is suspected. (5.6)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of NUCYNTA tablets in patients with circulatory shock. (5.8)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of NUCYNTA tablets in patients with impaired consciousness or coma. (5.9)

I. September 2018 Label

1. Revisions made to **boxed warning** to note that the FDA has required a REMS for Nucynta.

2016 Boxed Warning

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- NUCYNTA tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)
- To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.3)
- Accidental ingestion of NUCYNTA tablets, especially by children, can result in a fatal overdose of tapentadol. (5.3)
- Prolonged use of NUCYNTA tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation (5.5), (7).

JANSSEN
LABEL CHANGES FOR NUCYNTA ER
(NDA 200533)

SUMMARY OF LABEL CHANGES

- I. August 25, 2011 Initial Label**⁴⁴
- II. July 2012 Label**⁴⁵
1. Addition of “Limitations of Use” section made to **INDICATIONS AND USAGE**.
 2. Additional warnings added to **Boxed Warning**
 3. Revisions made to **WARNINGS AND PRECAUTIONS** to remove warnings
- III. August 2012 Label**⁴⁶
1. Indication added to **INDICATIONS AND USAGE**.
- IV. April 2014 Label**⁴⁷
1. Revisions made to **INDICATIONS AND USAGE**
 2. Additional warnings added to **Boxed Warning**
- V. September 2018 Label**⁴⁸
1. Revisions made to **Boxed Warning** adding information and additional warnings
 2. Revisions made to existing warnings and additional warnings added to **WARNINGS AND PRECAUTIONS**

⁴⁴ JAN-MS-02544901

⁴⁵ JAN-MS-00229587

⁴⁶ JAN-MS-00229558

⁴⁷ JAN-MS-03088328

⁴⁸ Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/200533s018s019lbl.pdf (last visited March 21, 2019)

DETAILED REVIEW OF LABEL CHANGES

I. August 25 2011, Initial Label

1. Approved INDICATION AND USAGE.

2011 Package Insert

INDICATIONS AND USAGE

NUCYNTA[®] ER is an opioid analgesic indicated for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

2. Approved Boxed Warning.

2011 Boxed Warning

WARNING: Potential for Abuse, proper patient selection and limitations of use

See full prescribing information for complete boxed warning.

NUCYNTA[®] ER contains tapentadol, a mu-opioid agonist and Schedule II controlled substance, with risk of misuse, abuse, and diversion similar to other opioid analgesics. (5.5)

NUCYNTA[®] ER is not intended for use as an as-needed analgesic (1).

NUCYNTA[®] ER is not intended for the management of acute or postoperative pain (1)

Swallow NUCYNTA[®] ER tablets whole. Taking split, broken, chewed, dissolved, or crushed NUCYNTA[®] ER tablets could lead to rapid release and absorption of a potentially fatal dose of tapentadol. (5.1)

Patients must not consume alcoholic beverages, prescription or non-prescription medications containing alcohol. Co-ingestion of alcohol with NUCYNTA[®] ER may result in a potentially fatal overdose of tapentadol.(12.3)

3. Approved **WARNINGS AND PRECAUTIONS**

2011 Package Insert
<p style="text-align: center;">— WARNINGS AND PRECAUTIONS —</p> <ul style="list-style-type: none"> • Respiratory depression: Increased risk in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction. (5.2) • CNS effects: Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.3) • Elevation of intracranial pressure: Use with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure. (5.4) • Abuse potential may occur. Monitor patients closely for signs of abuse and addiction. (5.5) • Hypotension may occur, particularly in patients at high risk (5.6) • Impaired mental/physical abilities: Caution must be used with potentially hazardous activities. (5.7) • Interaction with alcohol and drugs of abuse: CNS, respiratory depression, hypotension and sedation effects may be additive (5.8) • Seizures: Use with caution in patients with a history of seizures. (5.9) • Serotonin Syndrome: Potentially life-threatening condition could result from concomitant administration of drugs with serotonergic activity. (5.10) • Withdrawal symptoms may occur if NUCYNTA® ER is discontinued abruptly. Tapering may reduce withdrawal symptoms. (5.11)

II. July 2012 Label

1. Addition of “Limitations of Use” section made to **INDICATIONS AND USAGE** adding that it is not for use as needed, for acute pain. Qualified limitation of usage for postoperative pain also added.

2012 Package Insert

INDICATIONS AND USAGE

NUCYNTA® ER is an opioid agonist indicated for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

Limitations of Use

- NUCYNTA® ER is not for use:
 - As an as-needed (prn) analgesic (1)
 - For pain that is mild or not expected to persist for an extended period of time (1)
 - For acute pain (1)
 - For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time (1)

2. Additions made to **Boxed Warning** regarding fatal respiratory depression, fatal overdose from accidental ingestion, and instructing patients to not consume alcohol products while taking Nucynta ER.

2012 Boxed Warning

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, ACCIDENTAL EXPOSURE, and INTERACTION WITH ALCOHOL

See full prescribing information for complete boxed warning.

- NUCYNTA® ER contains tapentadol, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during NUCYNTA® ER therapy. (5.1)
- Fatal respiratory depression may occur, with highest risk at initiation and with dose increases. Instruct patients on proper administration of NUCYNTA® ER tablets to reduce the risk. (5.2)
- Accidental ingestion of NUCYNTA® ER can result in fatal overdose of tapentadol, especially in children. (5.3)
- Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while taking NUCYNTA® ER because of the risk of increased and potentially fatal plasma tapentadol levels. (5.4)

3. Revisions made to **WARNINGS AND PRECAUTIONS** to remove warnings regarding abuse potential, withdrawal, and impaired mental/physical abilities.

2012 Package Insert

WARNINGS AND PRECAUTIONS

- Respiratory depression: Increased risk in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction. (5.2)
- CNS effects: Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.3)
- Elevation of intracranial pressure: Use with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure. (5.4)
- Abuse potential may occur. Monitor patients closely for signs of abuse and addiction. (5.5)
- Hypotension may occur, particularly in patients at high risk (5.6)
- Impaired mental/physical abilities: Caution must be used with potentially hazardous activities. (5.7)
- Interaction with alcohol and drugs of abuse: CNS, respiratory depression, hypotension and sedation effects may be additive (5.8)
- Seizures: Use with caution in patients with a history of seizures. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant administration of drugs with serotonergic activity. (5.10)
- Withdrawal symptoms may occur if NUCYNTA® ER is discontinued abruptly. Tapering may reduce withdrawal symptoms. (5.11)

III. August 2012 Label

1. Specific indication added for pain related to diabetic peripheral neuropathy to **INDICATIONS AND USAGE**.

2012 Package Insert
<p style="text-align: center;">INDICATIONS AND USAGE</p> <p>NUCYNTA® ER is an opioid agonist indicated for the management of:</p> <ul style="list-style-type: none"> • moderate to severe chronic pain in adults (1) • neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults (1) <p>when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • NUCYNTA® ER is not for use: <ul style="list-style-type: none"> – As an as-needed (prn) analgesic (1) – For pain that is mild or not expected to persist for an extended period of time (1) – For acute pain (1) – For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. (1)

IV. April 2014 Label

1. Revisions made to **INDICATIONS AND USAGE** revising "moderate to severe pain" to "pain severe enough ...".

2014 Package Insert
<p style="text-align: center;">INDICATIONS AND USAGE</p> <p>NUCYNTA® ER is an opioid agonist indicated for the management of:</p> <ul style="list-style-type: none"> • pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1) • neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1) <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve NUCYNTA® ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • NUCYNTA® ER is not indicated as an as-needed (prn) analgesic. (1)

2. Additional warnings added to **Boxed Warning** adding warning regarding the prolonged use of Nucynta ER during pregnancy can result in neonatal opioid withdrawal syndrome.

2014 Boxed Warning

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL

See full prescribing information for complete boxed warning.

- NUCYNTA[®] ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow NUCYNTA[®] ER tablets whole to avoid exposure to a potentially fatal dose of tapentadol. (5.2)
- Accidental ingestion of NUCYNTA[®] ER, especially in children, can result in fatal overdose of tapentadol. (5.2)
- Prolonged use of NUCYNTA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3).
- Instruct patients not to consume alcohol or any products containing alcohol while taking NUCYNTA[®] ER because co-ingestion can result in fatal plasma tapentadol levels. (5.4)

V. September 2018 Label

1. Revisions made to **Boxed Warning** adding information regarding the FDA requiring a REMS for opioid analgesics and additional warnings regarding concomitant uses of opioids with CNS depressants

2018 Boxed Warning

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE- THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- NUCYNTA ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)
- To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow NUCYNTA ER tablets whole to avoid exposure to a potentially fatal dose of tapentadol. (5.3)
- Accidental ingestion of NUCYNTA ER, especially in children, can result in fatal overdose of tapentadol. (5.3)
- Prolonged use of NUCYNTA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.4).
- Instruct patients not to consume alcohol or any products containing alcohol while taking NUCYNTA ER because co-ingestion can result in fatal plasma tapentadol levels. (5.5)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.5), (7).

2. Revisions made to existing warnings regarding hypotension, noting severe hypotension and avoiding use of Nucynta ER in patients with circulatory shock, and additional warnings for adrenal insufficiency added to

WARNINGS AND PRECAUTIONS

2018 Package Insert

WARNINGS AND PRECAUTIONS

- Risk of Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.1)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue NUCYNTA ER if serotonin syndrome is suspected. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of NUCYNTA ER in patients with circulatory shock. (5.9)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of NUCYNTA ER in patients with impaired consciousness or coma. (5.10)

TEVA
LABEL CHANGES FOR ACTIQ
(NDA 020747)

SUMMARY OF LABEL CHANGES

- X. November 4, 1998 Initial Label**⁴⁹
- XI. September 24, 2004 Label**⁵⁰
1. No major changes
- XII. September 6, 2006 Label**⁵¹
1. Additional warning added to **BOXED WARNING**
 2. Additional warnings added to **CLINICAL PHARMACOLOGY AND PHARMACOKINETICS**
 3. Minor edits made to **INDICATIONS AND USAGE**
 4. Additional warnings added to **PRECAUTIONS**
- XIII. February 7, 2007 Label**⁵²
1. No major changes
- XIV. November 9, 2009 Label**⁵³
1. Additional warning added to **BOXED WARNING**
- XV. July 20, 2011 Label**⁵⁴
1. Additional warnings added to **WARNINGS AND PRECAUTIONS** to add Actiq REMS Program
- XVI. December 28, 2011 Label**⁵⁵
1. Addition of “Limitations of Use” section made to **INDICATIONS AND USAGE**

⁴⁹ See Actiq FDA labels, available at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020747> (last visited March 24, 2019)

⁵⁰ *Id.*

⁵¹ *Id.*

⁵² *Id.*

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ *Id.*

2. Additional warnings added to **WARNINGS AND PRECAUTIONS** to include TIRF REMS Access Program

XVII. December 16, 2016 Label⁵⁶

1. Additional warnings added to **BOXED WARNING**
2. Additional warnings added to **DOSAGE AND ADMINISTRATION**
3. Additional warnings added to **CONTRAINDICATIONS**
4. Additional warnings added to **WARNINGS AND PRECAUTIONS**

⁵⁶ *Id.*

DETAILED REVIEW OF CERTAIN ACTIQ LABEL CHANGES

I. 1998 Initial Actiq Label

1. Approved "Indication and Usage"

INDICATIONS AND USAGE

(See BOX WARNING and CONTRAINDICATIONS)

Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 µg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

Actiq is intended to be used only in the care of cancer patients only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

2. Approved Black Box Warning

CII

**PHYSICIANS AND OTHER HEALTHCARE PROVIDERS
MUST BECOME FAMILIAR WITH THE IMPORTANT
WARNINGS IN THIS LABEL.**

Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 µg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

Actiq is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

WARNING: May be habit forming

3. Approved “Drug Abuse and Dependence” Section

DRUG ABUSE AND DEPENDENCE

Fentanyl is a mu-opioid agonist and a Schedule II controlled substance that can produce drug dependence of the morphine type. *Actiq* may be subject to misuse, abuse and addiction.

The administration of *Actiq* should be guided by the response of the patient. Physical dependence, per se, is not ordinarily a concern when one is treating a patient with chronic cancer pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

The handling of *Actiq* should be managed to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law (see **SAFETY AND HANDLING**).

II. 2006 Actiq Label

1. Modification of “Indications and Usage” Section

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. For this reason, *Actiq* is contraindicated in the management of acute or postoperative pain.

2. Modification of Black Box Warning

PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. *ACTIQ* can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing *ACTIQ* in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

ACTIQ[®] is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *ACTIQ* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that *ACTIQ* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions).

III. 2011 Actiq Label

1. Modification of “Indications and Usage” Section

I INDICATIONS AND USAGE

ACTIQ (oral transmucosal fentanyl citrate) is indicated for the management of breakthrough pain in cancer patients 16 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid

tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids when taking *ACTIQ*.

This product **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, *ACTIQ* is contraindicated in the management of acute or postoperative pain.

ACTIQ is intended to be used only in the care of opioid-tolerant cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Limitations of Use;

As a part of the TIRF REMS Access program, ACTIQ may be dispensed only to outpatients enrolled in the program [see *Warnings and Precautions (5.10)*]. For inpatient administration of ACTIQ (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2. Modification of Boxed Warning

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

RESPIRATORY DEPRESSION

Fatal respiratory depression has occurred in patients treated with ACTIQ, including following use in opioid non-tolerant patients and improper dosing. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. [see *Contraindications (4)*]

Death has been reported in children who have accidentally ingested ACTIQ. ACTIQ must be kept out of reach of children. [see *Patient Counseling Information (17.3)* and *How Supplied/Storage and Handling (16.1)*]

The concomitant use of ACTIQ with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see *Drug Interactions (7)*].

MEDICATION ERRORS

Substantial differences exist in the pharmacokinetic profile of ACTIQ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose.

- When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to ACTIQ. (2.1)

- When dispensing, do not substitute an ACTIQ prescription for other fentanyl products.

ABUSE POTENTIAL

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program. [see *Warnings and Precautions (5.10)*] Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

3. Modification of “Drug Abuse and Dependence” Section

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl is a Schedule II controlled substance that can produce drug dependence of the morphine type. ACTIQ may be subject to misuse, abuse and addiction.

9.2 Abuse and Addiction

Manage the handling of ACTIQ to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law *[see How Supplied/Storage and Handling (16.1, 16.2)]*.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. “Drug-seeking” behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since ACTIQ may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Guide the administration of ACTIQ by the response of the patient.

Physical dependence, per se, is not ordinarily a concern when one is treating a patient with chronic cancer pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

IV. 2016 Actiq Label

1. Modification of Boxed Warning

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISKS FROM CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

Life-Threatening Respiratory Depression

Serious, life threatening and/or fatal respiratory depression has occurred in patients treated with ACTIQ, including following use in opioid non-tolerant patients and improper dosing. Monitor for respiratory depression, especially during initiation of ACTIQ or following a dose increase [see Warnings and Precautions (5.1)]. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose [see Warnings and Precautions (5.2)].

Due to the risk of respiratory depression, ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients [see Contraindications (4)].

Accidental Ingestion

Accidental ingestion of even one dose of ACTIQ, especially by children, can result in a fatal overdose of fentanyl [see Warnings and Precautions (5.2)].

Death has been reported in children who have accidentally ingested ACTIQ. ACTIQ must be kept out of reach of children [see Patient Counseling Information and How Supplied/Storage and Handling (16)].

Cytochrome P450 3A4 Interaction

The concomitant use of ACTIQ with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving ACTIQ and any CYP3A4 inhibitor or inducer [see Warnings and Precautions (5.3), Drug Interactions (7), Clinical Pharmacology (12.3)].

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.4), Drug Interactions (7)].

- Reserve concomitant prescribing of ACTIQ and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Risk of Medication Errors

Substantial differences exist in the pharmacokinetic profile of ACTIQ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl and that could result in fatal overdose [see *Dosage and Administration* (2.1), *Warnings and Precautions* (5.5)].

- When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to ACTIQ [see *Dosage and Administration* (2.1)].
- When dispensing, do not substitute an ACTIQ prescription for other fentanyl products.

Addiction, Abuse, and Misuse

ACTIQ exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ACTIQ, and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions* (5.6)].

Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program [see *Warnings and Precautions* (5.7)]. Further information is available at www.TIRFREMSAccess.com or by calling 1 866 822 1483.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of ACTIQ during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions* (5.8)].

1 INDICATIONS AND USAGE**2. Modification of “Drug Abuse and Dependence” Section****5.6 Addiction, Abuse, and Misuse**

ACTIQ contains fentanyl, a Schedule II controlled substance. As an opioid, ACTIQ exposes users to the risks of addiction, abuse, and misuse [see *Drug Abuse and Dependence* (9)].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed ACTIQ. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing ACTIQ, and monitor all patients receiving ACTIQ for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as ACTIQ, but use in such patients necessitates intensive counseling about the risks and proper use of ACTIQ along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing ACTIQ. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see *Patient Counseling Information* (17)]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

TEVA
LABEL CHANGES FOR FENTORA
(NDA 021947)

SUMMARY OF LABEL CHANGES

- I. September 25, 2006 Initial Label**⁵⁷
- II. March 3, 2007 Label and April 27, 2007 Label**⁵⁸
 1. No changes
- III. February 7, 2008 Label**⁵⁹
 1. Edits made to phrasing in **INDICATIONS AND USAGE**
 2. Additional warnings added to **BOXED WARNING**
 3. Additional warnings added to **WARNINGS AND PRECAUTIONS**
- IV. December 2, 2009 Label**⁶⁰
 1. Additional warnings added to **WARNINGS AND PRECAUTIONS**
- V. January 1, 2011 Label**⁶¹
 1. Additional warnings added to **DRUG ABUSE AND DEPENDENCE**
- VI. December 28, 2011 Label**⁶²
 1. Addition of “Limitations of Use” section made to **INDICATIONS AND USAGE**.
 2. Additional warnings added to **BOXED WARNING**
 3. Additional warnings added to **WARNINGS AND PRECAUTIONS** to include TIRF REMS Access Program

⁵⁷ See Fentora FDA Labels, *available at* <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021947> (March 24, 2009)

⁵⁸ *Id.*

⁵⁹ *Id.*

⁶⁰ *Id.*

⁶¹ *Id.*

⁶² *Id.*

VII. February 21, 2013 Label⁶³

1. Additional warnings added to **SPECIFIC POPULATIONS: PREGNANCY AND NEONATAL**
2. Additional warnings added to **DRUG ABUSE AND DEPENDENCE**
3. Additional warning added to **DOSAGE AND ADMINISTRATION**

VIII. December 16, 2016 Label⁶⁴

1. Additional warnings added to **BOXED WARNING**
2. Additional warnings added to **WARNINGS AND PRECAUTION**
3. Edits and additions made to **SPECIFIC POPULATIONS: PREGNANCY AND NEONATAL**
4. Edits made to **OVERDOSAGE**
5. Additional warnings added to **DOSAGE AND ADMINISTRATION**

⁶³ *Id.*

⁶⁴ *Id.*

DETAILED REVIEW OF CERTAIN FENTORA LABEL CHANGES

I. 2006 Initial Label

1. Approved “Indication and Usage”

INDICATIONS AND USAGE

(See BOXED WARNING and CONTRAINDICATIONS)

FENTORA is indicated for the management of breakthrough pain in patients with cancer who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation could occur at any dose in patients not on a chronic regimen of opiates. For this reason, *FENTORA* is contraindicated in the management of acute or postoperative pain.

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

2. Approved Black Box Warning

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. *FENTORA* can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing *FENTORA* in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

FENTORA is indicated for the management of breakthrough pain in patients with cancer who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, *FENTORA* is **contraindicated** in the management of acute or postoperative pain. **This product is not indicated for use in opioid non-tolerant patients.**

Patients and their caregivers must be instructed that *FENTORA* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. (See Information for Patients and Their Caregivers for disposal instructions.)

Due to the higher bioavailability of fentanyl in *FENTORA*, when converting patients from other oral fentanyl products, including oral transmucosal fentanyl citrate (OTFC and Actiq®), to *FENTORA*, do not substitute *FENTORA* on a mcg per mcg basis. Adjust doses as appropriate (see DOSAGE AND ADMINISTRATION).

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

3. Approved “Contraindications” Section

CONTRAINDICATIONS

Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, *FENTORA* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

FENTORA is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

4. Approved “Drug Abuse and Addiction” Section

Drug Abuse, Addiction and Diversion of Opioids

FENTORA contains fentanyl, a mu -opioid agonist and a Schedule II controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse, and criminal diversion.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

“Drug-seeking” behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Since *FENTORA* tablets may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

FENTORA should be handled appropriately to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Physical Dependence and Withdrawal

The administration of *FENTORA* should be guided by the response of the patient.

Physical dependence, per se, is not ordinarily a concern when one is treating a patient with cancer and chronic pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

5. Approved “Information for Patients and Caregivers” Section

Information for Patients and Their Caregivers

...

11. Patients should be warned that the active ingredient in *FENTORA* is fentanyl which is a drug that some people abuse. *FENTORA* should be taken only by the patient it was prescribed for, and it should be protected from theft or misuse in the work or home environment.

II. 2008 Fentora Label

1. Modification of “Indications and Usage” Section

INDICATIONS AND USAGE

(See **BOXED WARNING** and **CONTRAINDICATIONS**.)

FENTORA is indicated only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, *FENTORA* is contraindicated in the management of acute or postoperative pain.

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

2. Modification of Black Box Warning

Reports of serious adverse events, including deaths in patients treated with *FENTORA* have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of *FENTORA* for any other fentanyl product may result in fatal overdose.

FENTORA is indicated only for the management of breakthrough pain in patients with cancer who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily or a week or longer.

FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from Actiq[®] to *FENTORA*. Carefully consult the Initial Dosing Recommendations table. (See DOSAGE AND ADMINISTRATION, Table 7.)

When dispensing, do not substitute a *FENTORA* prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of *FENTORA* compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of *FENTORA* for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing *FENTORA*. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose. (See **DOSAGE AND ADMINISTRATION**.)

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. *FENTORA* can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing *FENTORA* in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that *FENTORA* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. (See Information for Patients and Caregivers for disposal instructions.)

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of *FENTORA* with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

III. January 2011 Fentora Label

1. Modification of “Drug Abuse and Addiction” Section

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FENTORA contains fentanyl, a *mu*-opioid agonist and a Schedule II controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse and criminal diversion.

9.2 Abuse and Addiction

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. “Drug-seeking” behavior is very common in addicts and drug abusers. FENTORA should be prescribed with caution to patients who have a higher risk of substance abuse, including patients with bipolar disorder and/or schizophrenia.

Patients with chronic pain may be at a higher risk for suicide.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Since FENTORA tablets may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Handle FENTORA appropriately to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Physical Dependence and Withdrawal

The administration of FENTORA should be guided by the response of the patient. Physical dependence, per se, is not ordinarily a concern when one is treating a patient with cancer and chronic pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

IV. December 2011 Fentora Label

1. Modification of “Indications and Usage” Section (Excerpt)

Limitations of Use:

As a part of the TIRF REMS Access program, FENTORA may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.11)]*. For inpatient administration of FENTORA (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2. Modification of Black Box Warning (Excerpt)

When dispensing, do not substitute a FENTORA prescription for other fentanyl products.

ABUSE POTENTIAL

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

Because of the risk for misuse, abuse, addiction, and overdose, FENTORA is available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program. *[see Warnings and Precautions (5.11)]* Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

3. Addiction of TIRF REMS Section

potentiation by TIRF inhibitors has been reported with opioid analgesics.

5.11 Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk for misuse, abuse, addiction, and overdose [see *Drug Abuse and Dependence (9)*], FENTORA is available only through a restricted program called the TIRF REMS Access program. Under the TIRF REMS Access program, outpatients, healthcare professionals who prescribe for outpatient use, pharmacies, and distributors must enroll in the program. For inpatient administration (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of FENTORA, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access program are:

- Healthcare professionals, who prescribe FENTORA for outpatient use, must review the prescriber educational materials for the TIRF REMS Access program, enroll in the program, and comply with the REMS requirements.
- To receive FENTORA, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense FENTORA must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute FENTORA must enroll in the program, and distribute only to authorized pharmacies.

V. 2013 Fentora Label

1. Modification of “Drug Abuse and Dependence” Section

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FENTORA contains fentanyl, a *mu*-opioid agonist and a Schedule II controlled substance with high potential for abuse similar to other opioids including hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse and criminal diversion.

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated abuse of a prescription drug and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, and sometimes tolerance and/or physical dependence.

Abuse and addiction are separate and distinct from physical dependence and tolerance (see section 9.3). Physicians should be aware that addiction may not be accompanied by concurrent tolerance and physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Abuse of FENTORA poses a risk of overdose and death. This risk is increased with concurrent abuse of FENTORA with alcohol and other substances.

FENTORA, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy.

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use. Withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug constitute evidence of physical dependence. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine). Clinically significant physical dependence may not occur until after several days to weeks of continued opioid usage.

FENTORA should not be abruptly discontinued [*see Dosage and Administration (2.5)*]. If FENTORA is abruptly discontinued, or the dosage is rapidly reduced, in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms [*see Use in Specific Populations (8.1)*].

2. Addiction of “Addiction, Abuse and Misuse” Section

5.6 Addiction, Abuse, and Misuse

FENTORA contains fentanyl, a Schedule II controlled substance. As an opioid, FENTORA exposes users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed FENTORA. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing FENTORA, and monitor all patients receiving FENTORA for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as FENTORA, but use in such patients necessitates intensive counseling about the risks and proper use of FENTORA along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing FENTORA. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

3. Addiction of Neonatal Withdrawal Syndrome Section

5.8 Neonatal Opioid Withdrawal Syndrome

Prolonged use of FENTORA during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [*see Use in Specific Populations (8.1), Patient Counseling Information (17)*].

ACTAVIS
LABEL CHANGES FOR KADIAN
(NDA 020616)

SUMMARY OF LABEL CHANGES

I. July 3, 1996 Initial Label⁶⁵

II. July 29, 1997⁶⁶

1. Labeling revision. The supplemental application provides for an alternate method of administration of the pellets contained in KADIAN for patients who have difficulty swallowing whole capsules. The method is to sprinkle the pellets on to soft food as the polymer-coated delivery system allows the option of opening the capsules.

III. April 8, 1998⁶⁷

1. Package change.

IV. July 16, 1999⁶⁸

1. Labeling revision providing an alternative route of administration of capsule content via GI Tube.

V. September 28, 2005⁶⁹

1. Package change. Supplemental NDA was filed on January 31, 2003. Additional submissions were submitted May 23, 2003, August 19, 2003, and April 1, 2005. This “Changes Being Effected in 30 days” supplemental new drug application provided for updated information on blister packaging and was approved on September 28, 2005.

VI. October 27, 2006⁷⁰

⁶⁵ ALLERGAN_MDL_00299219-241

⁶⁶ ALLERGAN_MDL_03298341; ALLERGAN_MDL_02505667

⁶⁷ See Kadian Labels. *available at*,

<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020616> (last visited March 22, 2019)

⁶⁸ ALLERGAN_MDL_02284211; ALLERGAN_MDL_02843609

⁶⁹ See Kadian Labels. *available at*,

<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020616> (last visited March 22, 2019)

⁷⁰ *Id.*

1. Formulation revision. Supplemental NDA was filed on March 30, 2006 providing for 80-mg dosage strength of KADIAN. This application was approved on October 27, 2006. Added boxed warning.

VII. February 27, 2007⁷¹

1. Formulation revision. Supplemental NDAs were filed on December 23, 2004 and November 30, 2005. These applications provided for a reformulated 100-mg capsule and new 200-mg strength capsule. The applications were approved February 27, 2007.
2. Changes to the package insert are also made to include information about the *in vitro* finding that the extended-release characteristics of Kadian are compromised in the presence of alcohol and warnings about the potential for dose dumping *in vivo* if Kadian is taken concomitantly with alcohol.

VIII. April 20, 2007⁷²

1. Formulation revision. Supplemental NDA was filed on December 22, 2006 providing for 10-mg dosage strength of KADIAN. This application was approved on April 20, 2007.

IX. July 9, 2012⁷³

- FDA approved ER/LA Opioid Class REMS and standardized the package inserts for all ER/LA opioids.
- The language in **boxed warning** changed
- The limitation of usage language in the **INDICATION AND USAGE** section changed.
- The language in the **DOSAGE and ADMINISTRATION** section changed.
- The language in the **CONTRAINDICATIONS** section changed.
- New language on abuse potential added to the **WARNINGS AND PRECAUTIONS** section.
- Warning about respiratory depression in **WARNINGS AND PRECAUTIONS** was replaced with a warning of life threatening respiratory depression.
- Section 5.7 hypotensive effect warning added to the **WARNINGS AND PRECAUTIONS** section.
- Section 5.6 in **WARNINGS AND PRECAUTIONS** section was changed with a warning for interaction with CNS depressants, and alcohol or illicit drugs that cause CNS depression.

⁷¹ *Id.*

⁷² *Id.*

⁷³ *Id.*

- New section 5.4 and 5.5 Elderly, Cachectic, and Debilitated Patients and patients with chronic pulmonary disease monitoring was added to the **WARNINGS AND PRECAUTIONS** section.
- New language added to section 6.1 in **ADVERSE REACTION** section to address constipation, nausea, and somnolence.

X. March 27, 2013⁷⁴

1. Labeling revisions. Supplemental NDA was filed on January 2, 2013. This “Changes Being Effected” supplemental new drug application provided for revised container labels for KADIAN 100 mg, 130 mg, 150 mg, and 200 mg, to include a flag that states, “**FOR UES IN OPIOID TOLERANT PATIENTS ONLY.**” The revised container label was approved on March 27, 2013.

XI. April 16, 2014⁷⁵

1. The Abuse Potential warning in **Boxed Warnings** was replaced with an Addiction, Abuse, and Misuse warning.
2. New **DOSAGE AND ADMINISTRATION** language was added.
3. New warning regarding Neonatal Opioid Withdrawal Syndrome added to the **Boxed Warnings**.
4. The indication in **INDICATIONS AND USAGE** section was narrowed to severe pain for which other treatment options are inadequate.
5. Changes made to the addiction abuse and misuse language in the **WARNINGS AND PRECAUTIONS** section.
6. A new warning regarding the risk of Neonatal Opioid Withdrawal Syndrome was added to the **WARNINGS AND PRECAUTIONS** section.

XII. August 19, 2014⁷⁶

- FDA approved new indication for ER/LA opioid analgesics.
- New warning for Neonatal Opioid Withdraw Syndrome (NOWS)
- Updated language for the following **WARNINGS AND PRECAUTIONS**: addiction, abuse, and misuse; life-threatening respiratory depression; accidental ingestion

XIII. June 26, 2015⁷⁷

1. Proposed modification to the REMS for Kadian were submitted and approved.

⁷⁴ *Id.*

⁷⁵ *Id.*

⁷⁶ *Id.*

⁷⁷ *Id.*

XIV. April 20, 2016⁷⁸

1. Proposed modification to the REMS for Kadian were submitted and approved.

XV. September 30, 2016⁷⁹

1. Proposed modification to the REMS for Kadian were submitted and approved.

XVI. December 16, 2016⁸⁰

- Risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants added to the **Boxed Warning**.
- A new section 5.9 was added with risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness in **WARNINGS AND PRECAUTIONS**
- A new section regarding risk of severe hypotension in patients with circulatory shock added to the **WARNINGS AND PRECAUTIONS** section.
- A new section 5.7 was added with Adrenal Insufficiency added to **WARNINGS AND PRECAUTIONS**.

XVII. May 26, 2017⁸¹

1. Proposed modification to the REMS for Kadian were submitted and approved.

XVIII. September 18, 2018⁸²

1. Information about REMS added to the **Boxed Warning**.
2. New section 5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) added to the **WARNINGS AND PRECAUTIONS** section.

⁷⁸ *Id.*

⁷⁹ *Id.*

⁸⁰ *Id.*

⁸¹ *Id.*

⁸² *Id.*

DETAILED REVIEW OF LABEL CHANGES

I. October 27, 2006

1. Approved Boxed Warning.

October 2006 Package Insert

WARNING:

KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

KADIAN® Capsules are NOT for use as a prn analgesic.

KADIAN® 100 mg Capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS

ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. KADIAN® CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLE SAUCE. THE PELLETS IN THE CAPSULES ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

2. New strengths of 80-mg added.

II. February 27, 2007

1. Formulation revision. Supplemental NDAs were filed on December 23, 2004 and November 30, 2005. These applications provided for a reformulated 100-mg capsule and new 200-mg strength capsule. The applications were approved February 27, 2007.
2. Changes to the package insert are also made to include information about the *in vitro* finding that the extended-release characteristics of Kadian are compromised in the presence of alcohol and warnings about the potential for dose dumping *in vivo* if Kadian is taken concomitantly with alcohol. The label did provide that:

Interactions with Alcohol and Drugs of Abuse

KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

III. April 20, 2007

1. New strength of 10-mg added.

IV. July 9, 2012

1. FDA approved ER/LA Opioid Class REMS and standardized the package inserts for all ER/LA opioids.
2. The **Boxed Warning** language was changed almost in its entirety.

2012 Package Insert

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

KADIAN contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit [see Warnings and Precautions (5.1)]. Assess each patient's risk for opioid abuse or addiction prior to prescribing KADIAN. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving KADIAN for signs of misuse, abuse, and addiction during treatment [see Drug Abuse and Dependence (9)].

Life-threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of KADIAN, even when the drug has been used as recommended and not misused or abused [see Warnings and Precautions (5.2)]. Proper dosing and titration are essential and KADIAN should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of KADIAN or following a dose increase. Instruct patients to swallow KADIAN capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine.

Accidental Exposure

Accidental consumption of KADIAN, especially in children, can result in a fatal overdose of morphine [see Warnings and Precautions (5.3)].

3. The Limitation of Usage language in the **INDICATIONS AND USAGE** section changed.

2012 Package Insert

Limitations of Use

Kadian is not for use:

- As an as-needed (prn) analgesic
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid-tolerant are those taking at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

4. The entire **DOSAGE AND ADMINISTRATION** section has been reworked but no significant substantive changes were made.
5. A new Section 5.1 Abuse Potential added to **WARNINGS AND PRECAUTIONS**.
- 6.

2012 Package Insert

KADIAN contains morphine, an opioid agonist and a Schedule II controlled substance. Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing KADIAN in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient's risk for opioid abuse or addiction prior to prescribing KADIAN. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of KADIAN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death [see Overdosage (10)]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

7. Section 5.2 Respiratory Depression in **WARNINGS AND PRECAUTIONS** section was replaced with Section 5.2 Life Threatening Respiratory Depression.

2012 Package Insert

Respiratory depression is the primary risk of KADIAN. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see Overdosage (10)].

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of KADIAN, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with KADIAN and following dose increases. Instruct patients against use by individuals other than the patient for whom KADIAN was prescribed and to keep KADIAN out of the reach of children, as such inappropriate use may result in fatal respiratory depression.

To reduce the risk of respiratory depression, proper dosing and titration of KADIAN are essential [see Dosage and Administration (2.1, 2.2)]. Overestimating the KADIAN dose when converting patients from another opioid product can result in fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-release opioids when used as recommended and not misused or abused.

To further reduce the risk of respiratory depression, consider the following:

- Proper dosing and titration are essential and KADIAN should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. KADIAN 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant patients only. Ingestion of this strength of KADIAN capsules or of the pellets within the capsule may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids.
- Instruct patients to swallow KADIAN capsules intact or to sprinkle the capsule contents on applesauce and swallow without chewing. The pellets in the capsules are not to be crushed, dissolved, or chewed. The resulting morphine dose may be fatal, particularly in opioid-naïve individuals.
- KADIAN is contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression [see Contraindications (4)].

8. New section on accidental exposure added to **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

Accidental consumption of KADIAN, especially in children, can result in a fatal overdose of morphine.

9. New section 5.4 Elderly, Cachectic, and Debilitated Patients was added to **WARNINGS AND PRECAUTIONS**.

2012 Package Insert

Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance compared to younger, healthier patients. Therefore, monitor such patients closely, particularly when initiating and titrating KADIAN and when KADIAN is given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.2)].

10. A new Section 5.5 Use in Patients with Chronic Pulmonary Disease was added to the **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with KADIAN, as in these patients, even usual therapeutic doses of KADIAN may decrease respiratory drive to the point of apnea [see Warnings and Precautions (5.2)]. Consider the use of alternative non-opioid analgesics in these patients if possible.

11. A new Section 5.6 Interactions with CNS Depressants and Illicit Drugs was added to **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

Hypotension, profound sedation, coma, or respiratory depression may result if KADIAN is used concomitantly with other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). When considering the use of KADIAN in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, consider the patient's use, if any, of alcohol or illicit drugs that cause CNS depression. If KADIAN therapy is to be initiated in a patient taking a CNS depressant, start with a lower KADIAN dose than usual and monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant [see Drug Interactions (7.2)].

12. A new Section 5.7 Hypotensive Effect was added to **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

KADIAN may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) [see Drug Interactions (7.2)]. Monitor these patients for signs of hypotension after initiating or titrating the dose of KADIAN. In patients with circulatory shock, KADIAN may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of KADIAN in patients with circulatory shock.

13. A new Section 5.8 Use in Patients with Head Injury or Increased Intracranial Pressure was added to **WARNINGS AND PRECAUTIONS** section.

2012 Package Insert

Monitor patients taking KADIAN who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with KADIAN. KADIAN may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of KADIAN in patients with impaired consciousness or coma.

V. March 27, 2013

1. This “Changes Being Effected” supplemental new drug application provides for revised container labels for KADIAN 100 mg, 130 mg, 150 mg, and 200 mg, to include a flag that states, “**FOR USE IN OPIOID TOLERANT PATIENTS ONLY.**”

VI. April 16, 2014

1. New **Boxed Warning.**

2014 Package Insert

**WARNING: ADDICTION, ABUSE, AND MISUSE;
LIFETHREATENING RESPIRATORY DEPRESSION;
ACCIDENTAL INGESTION NEONATAL OPIOID
WITHDRAWAL SYNDROME; and INTERACTION WITH
ALCOHOL**

See full prescribing information for complete boxed warning.

- **KADIAN exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow KADIAN capsules whole to avoid exposure to a potentially fatal dose of morphine. (5.2)**
- **Accidental ingestion of KADIAN, especially in children, can result in fatal overdose of morphine. (5.3)**
- **Prolonged use of KADIAN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3).**
- **Instruct patients not to consume alcohol or any products containing alcohol while taking KADIAN because co-ingestion can result in fatal plasma morphine levels. (5.4)**

2. The indication in **INDICATIONS AND USAGE** section was narrowed.

2014 Package Insert

KADIAN is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve KADIAN for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- KADIAN is not indicated as an as-needed (prn) analgesic.

3. New language added to **DOSAGE AND ADMINISTRATION/Initial Dosing** section.

2014 Package Insert

KADIAN 100 mg, 130 mg, 150 mg, and 200 mg capsules are only for patients in whom tolerance to an opioid of comparable potency has been established. Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg of morphine daily, at least 30 mg of oral

oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid. (2.1)

- For opioid-naïve patients, initiate treatment using an immediate-release morphine formulation and then convert patients to KADIAN. For opioid non-tolerant patients, initiate with a 30 mg capsule orally every 24 hours.

4. A new warning regarding the risk of Neonatal Opioid Withdrawal Syndrome was added to the **WARNINGS AND PRECAUTIONS** section.

2014 Package Insert

5.1 Addiction, Abuse, and Misuse

KADIAN contains morphine, a Schedule II controlled substance. As an opioid, KADIAN exposes users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*]. As modified-release products such as KADIAN deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of morphine present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed KADIAN and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing KADIAN, and monitor all patients receiving KADIAN for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of KADIAN for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as KADIAN, but use in such patients necessitates intensive counseling about the risks and proper use of KADIAN along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of KADIAN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of morphine and can result in overdose and death [*see Overdosage (10)*].

Opioid agonists such as KADIAN are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing KADIAN. Strategies to reduce

these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see *Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death.

Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see *Overdosage (10)*]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of KADIAN, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with KADIAN and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of KADIAN are essential [see *Dosage and Administration (2)*].

Overestimating the KADIAN dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental ingestion of even one dose of KADIAN, especially by children, can result in respiratory depression and death due to an overdose of morphine.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of KADIAN during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology

experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and

severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

5.4 Interactions with Central Nervous System Depressants

Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on KADIAN therapy. The co-ingestion of alcohol with KADIAN may result in increased plasma levels and a potentially fatal overdose of morphine [*see Clinical Pharmacology (12.3)*].

Hypotension, profound sedation, coma, respiratory depression, and death may result if KADIAN is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of KADIAN in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin KADIAN is made, start with a low dose of KADIAN (30 mg or lower) every 24 hours, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant [*see Drug Interactions (7)*].

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating KADIAN and when KADIAN is given concomitantly with other drugs that depress respiration [*see Warnings and Precautions (5.2)*].

5.11 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including KADIAN. In these patients, mixed agonists/antagonists and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing KADIAN, gradually taper the dose [*see Dosage and Administration (2.3)*]. Do not abruptly discontinue KADIAN.

VII. August 19, 2014

1. FDA approved new indication for ER/LA opioid analgesics.
2. New warning for Neonatal Opioid Withdraw Syndrome (NOWS)
3. Updated language for the following **WARNINGS AND PRECAUTIONS**: addiction, abuse, and misuse; life-threatening respiratory depression; accidental ingestion

VIII. December 16, 2016

1. Language regarding risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants added to the **Boxed Warning**.
2. A new section 5.7 was added with Adrenal Insufficiency added to **WARNINGS AND PRECAUTIONS**.
3. A new section 5.9 was added with risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness in **WARNINGS AND PRECAUTIONS**
4. New language regarding risk of severe hypotension in patients with circulatory shock added to the **WARNINGS AND PRECAUTIONS** section.

2016 Package Insert

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.4), Drug Interactions (7)]

- Reserve concomitant prescribing of KADIAN Injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

5. Section 5.7 Interactions with Central Nervous System Depressants Risks in **WARNINGS AND PRECAUTIONS** section was replaced with subsection 5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants.

2016 Package Insert

5.7 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

6. Section 5.9 regarding risk of intracranial pressure added to the **WARNINGS AND PRECAUTIONS** section.

2016 Package Insert

5.9 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), KADIAN may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with KADIAN. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of KADIAN in patients with impaired consciousness or coma.

IX. September 18, 2018

1. Information about REMS added to the **Boxed Warning**.

2018 Package Insert

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration

(FDA) has required a REMS for these products [see Warnings and Precautions (5.2)]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to • complete a REMS-compliant education program, • counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products, • emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and • consider other tools to improve patient, household, and community safety.

2. Information about the REMS added to the **WARNINGS AND PRECAUTIONS** section.

2018 Package Insert

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link:
www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities. To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

MALLINCKRODT
LABEL CHANGES FOR EXALGO ER
(NDA 021217)

SUMMARY OF LABEL CHANGES

- I. March 2, 2010 Initial Label**⁸³
- II. August 27, 2012**⁸⁴
 - 1. Limitations of use added
 - 2. Revisions made to Boxed Warning
- III. March 2013**⁸⁵
 - 1. Revisions made to Boxed Warning
- IV. June 2014**⁸⁶
 - 1. Definition of opioid tolerant patient added and limitations of usage revised to mention abuse, misuse, and addiction.
 - 2. Neonatal withdrawal syndrome added to Boxed warnings
- V. December 2016**⁸⁷
 - 1. Boxed warning added warning re concomitant use of CNS depressants
- VI. September 2018**⁸⁸
 - 1. Boxed warning revised to note that the FDA has required a REMS.

⁸³ See Exalgo FDA Labels, *available at* <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021217> (last visited March 24, 2019)

⁸⁴ *Id.*

⁸⁵ *Id.*

⁸⁶ *Id.*

⁸⁷ *Id.*

⁸⁸ *Id.*

DETAILED REVIEW OF LABEL CHANGES

VII. March 2, 2010 Initial Label

- Approved **INDICATION AND USAGE.**

<p>EXALGO is an opioid agonist indicated for once daily administration for</p> <ul style="list-style-type: none"> • The management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time • EXALGO is NOT intended for use as an as needed analgesic

- Approved **Boxed Warning.**

<p>WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, LIMITATION OF USE, AND POTENTIAL FOR ABUSE <i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> • EXALGO is indicated for opioid tolerant patients only. (1) • EXALGO contains hydromorphone, a Schedule II controlled substance, which can be abused and is subject to misuse, abuse, addiction, and criminal diversion. (9) • EXALGO is not indicated for use in the management of acute or postoperative pain and is not intended for use as an as needed analgesic. (4) • Fatal respiratory depression could occur in patients who are not opioid tolerant. (5) • Accidental consumption of EXALGO, especially in children, can result in a fatal overdose of hydromorphone. (5) • EXALGO tablets are to be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected. Taking broken, chewed, dissolved or crushed EXALGO leads to rapid release and absorption of a potentially fatal dose of hydromorphone (5)

VIII. August 27, 2012 Label

1. Approved **INDICATION AND USAGE.**

<p>EXALGO is an opioid agonist indicated for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time (1).</p> <p>Limitations of Use</p> <p><input type="checkbox"/> EXALGO is not for use:</p> <p><input type="checkbox"/> As an as-needed (prn) analgesic (1)</p> <p><input type="checkbox"/> For pain that is mild or not expected to persist for an extended period of time (1)</p>

- ☐ For acute pain (1)
 - ☐ For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time (1)
- EXALGO is only for patients in whom tolerance to an opioid of comparable potency is established. (1)

2. Approved **Boxed Warning.**

<p>WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE <i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> • EXALGO contains hydromorphone, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during EXALGO therapy. (5.1, 9) • Fatal respiratory depression may occur, with highest risk at initiation and with dose increases; instruct patients on proper administration of EXALGO tablets to reduce risk. EXALGO is for use in opioid-tolerant patients only. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of hydromorphone. (5.2) • Accidental ingestion of EXALGO can result in fatal overdose of hydromorphone, especially in children. (5.3)

IX. March 2013 Label

1. Approved **INDICATION AND USAGE.**

<p style="text-align: center;">INDICATIONS AND USAGE</p> <p>EXALGO is an opioid agonist indicated for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time (1).</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • EXALGO is not for use: <ul style="list-style-type: none"> – As an as-needed (prn) analgesic (1) – For pain that is mild or not expected to persist for an extended period of time (1) – For acute pain (1) – For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time (1) <p>EXALGO is only for patients in whom tolerance to an opioid of comparable potency is established. (1)</p>

2. Approved **Boxed Warning.**

<p>WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE <i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> • EXALGO contains hydromorphone, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during EXALGO therapy. (5.1, 9) • Fatal respiratory depression may occur, with highest risk at initiation and with dose increases; instruct patients on proper administration of EXALGO tablets to reduce risk. EXALGO is for use in opioid-tolerant patients only. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of hydromorphone. (5.2) • Accidental ingestion of EXALGO can result in fatal overdose of hydromorphone, especially in children. (5.3) 	

X. **June 2014 Label**

1. Approved **INDICATION AND USAGE.**

<p style="text-align: center;">INDICATIONS AND USAGE</p> <p>Hydromorphone hydrochloride extended-release tablets are an opioid agonist indicated in opioid-tolerant patients for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.</p> <p>Patients considered opioid tolerant are those who are taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve hydromorphone hydrochloride extended-release tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Hydromorphone hydrochloride extended-release tablets are not indicated as an as-needed (prn) analgesic. 	

2. Approved **Boxed Warning.**

<p>WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; and NEONATAL OPIOID WITHDRAWAL SYNDROME <i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> Hydromorphone hydrochloride extended-release tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1) Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow hydromorphone hydrochloride extended-release tablets whole to avoid exposure to a potentially fatal dose of hydromorphone. (5.2) Accidental ingestion of hydromorphone hydrochloride extended-release tablets, especially in children, can result in fatal overdose of hydromorphone. (5.2) Prolonged use of hydromorphone hydrochloride extended-release tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3).

XI. December 2016 Label

1. Approved **INDICATION AND USAGE.**

<p style="text-align: center;">INDICATIONS AND USAGE</p> <p>EXALGO is an opioid agonist indicated in opioid-tolerant patients for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.</p> <p>Patients considered opioid tolerant are those who are taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve EXALGO for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. EXALGO is not indicated as an as-needed (prn) analgesic.

2. Approved **Boxed Warning**.

<p>WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS</p> <p><i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> • EXALGO exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and monitor regularly for these behaviors and conditions (5.1). • Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow EXALGO tablets whole to avoid exposure to a potentially fatal dose of hydromorphone (5.2). • Accidental ingestion of EXALGO, especially by children, can result in fatal overdose of hydromorphone (5.2). • Prolonged use of EXALGO during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3). • Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation (5.4, 7). 	

XII. September 2018 Label1. Approved **INDICATION AND USAGE**.

<p>INDICATION AND USAGE</p> <p>EXALGO is an opioid agonist indicated in opioid-tolerant patients for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.</p> <p>Patients considered opioid tolerant are those who are taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve EXALGO for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • EXALGO is not indicated as an as-needed (prn) analgesic. 	

2. Approved **Boxed Warning.**

<p>WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS</p> <p><i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> • EXALGO exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and monitor regularly for these behaviors and conditions. (5.1) • To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2) • Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow EXALGO tablets whole to avoid exposure to a potentially fatal dose of hydromorphone. (5.3) • Accidental ingestion of EXALGO, especially by children, can result in fatal overdose of hydromorphone. (5.3) • Prolonged use of EXALGO during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4) • Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.5, 7)

MALLINCKRODT
LABEL CHANGES FOR XARTEMIS XR
(NDA 204031)

SUMMARY OF LABEL CHANGES

- I. March 11, 2014 Initial Label**⁸⁹
- II. December 2016 Label Change**⁹⁰
 - 1. Boxed warnings revised to include additional warnings associated with concomitant use of Xartemis with CYP3A4 inhibitors and with CNS depressants.
- III. September 2018 Label Change**⁹¹
 - 1. Boxed warnings updated to include notice that FDA required Xartemis to be subject a REMS.

⁸⁹ See Xartemis XR FDA Labels, *available at* <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=204031> (last visited March 24, 2019)

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DETAILED REVIEW OF LABEL CHANGES

IV. March 11, 2014 Initial Label

- Approved **INDICATION AND USAGE**.

INDICATIONS AND USAGE
<p>XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets is a combination of oxycodone, an opioid agonist, and acetaminophen, and is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.</p> <p>Limitations of Use: Because of the risks of addiction, abuse, misuse, overdose, and death with opioids, even at recommended doses, reserve XARTEMIS XR for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate. (1)</p>

- Approved **Boxed Warning**.

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and HEPATOTOXICITY
<p><i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> • XARTEMIS XR exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1) • Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.2) • Accidental consumption of XARTEMIS XR, especially in children, can result in fatal overdose of oxycodone. (5.2) • Prolonged use of XARTEMIS XR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3) • XARTEMIS XR contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limit, and often involve more than one acetaminophen-containing product. (5.7, 5.11)

V. December 2016 Label Change

3. Approved **INDICATION AND USAGE.**

<p>-----INDICATIONS AND USAGE-----</p> <p>XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets is a combination of oxycodone, an opioid agonist, and acetaminophen, and is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.</p> <p><u>Limitations of Use:</u> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve XARTEMIS XR for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)</p>

4. Approved Boxed Warning.

<p>WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; HEPATOTOXICITY; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS</p> <p><i>See full prescribing information for complete boxed warning.</i></p> <ul style="list-style-type: none"> • XARTEMIS XR exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess risk before prescribing, and monitor regularly for these behaviors and conditions. (5.1) • Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.2) • Accidental Ingestion of XARTEMIS XR, especially in children, can result in fatal overdose of oxycodone. (5.2) • Prolonged use of XARTEMIS XR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3) • Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone. (5.4, 7, 12.3) • XARTEMIS XR contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product. (5.5, 5.12) • Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation [see Warnings and Precautions (5.6), Drug Interactions (7)]. 	
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VI. September 2018 Label Change

1. Approved INDICATION AND USAGE.

INDICATIONS AND USAGE
<p>XARTEMIS XR (oxycodone hydrochloride and acetaminophen) Extended-Release Tablets is a combination of oxycodone, an opioid agonist, and acetaminophen, and is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.</p> <p><u>Limitations of Use:</u> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve XARTEMIS XR for use in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)</p>

2. Approved **Boxed Warning**.

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; HEPATOTOXICITY; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- XARTEMIS XR exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess risk before prescribing, and monitor regularly for these behaviors and conditions. (5.1)
- To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.3)
- Accidental Ingestion of XARTEMIS XR, especially in children, can result in fatal overdose of oxycodone. (5.3)
- Prolonged use of XARTEMIS XR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone. (5.5, 7, 12.3)
- XARTEMIS XR contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product. (5.6, 5.13)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation [see *Warnings and Precautions* (5.7), *Drug Interactions* (7)].

MALLINCKRODT
LABEL CHANGES FOR OXYCODONE HYDROCHLORIDE
(ANDA 77822)

SUMMARY OF LABEL CHANGES⁹²

- I. July 24, 2008 Initial Label⁹³**
- II. July 2012 Label⁹⁴**
1. The **Boxed Warning** in the **Highlights of Prescribing Information** was changed to: “OxyContin contains oxycodone, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during OxyContin therapy.”
 2. The **Boxed Warning** in the **Full Prescribing Information** section was changed.
 3. Language on abuse was added to **Section 2.1 Initial Dosing**.
 4. A new **Section 2.2 Titration and Maintenance of Therapy** was added.
 5. A new **Section 5.1 Abuse Potential** was added.
 6. A new **Section 5.12 Avoidance of Withdrawal** was added.
 7. The language in **Section 9.2 Abuse** was substantially revised.
 8. **Section 9.3 Dependence** was changed.
 9. The language on abuse in **Section 17 Patient Counseling Information** was changed to: “Inform patients that OxyContin contains oxycodone, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share OxyContin with others and to take steps to protect OxyContin from theft or misuse.”
- III. April 16, 2013⁹⁵**
1. **Section 9.2 Abuse** was changed to add information on *Abuse Deterrence Studies*.
- IV. April 16, 2014⁹⁶**
1. The **Black Box Warning** in the **Highlights of Prescribing Information** was changed to: “OXYCONTIN exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess each patient’s

⁹² Changes track to label changes in brand-name Oxycontin as the “label is the same as the brand-name medicine’s label.” See Generic Drugs: Questions and Answers, *available at* <https://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm100100.htm> (last visited March 24, 2019)

⁹³ See MNK-T1_0004300013. Approval of the abbreviated new drug application for Mallinckrodt’s generic oxycodone hydrochloride extended release tablets.

⁹⁴ See Oxycontin FDA Labels, available at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=022272> (last visited March 24, 2019)

⁹⁵ *Id.*

⁹⁶ *Id.*

risk before prescribing and monitor regularly for development of these behaviors and conditions.”

2. The indication in **Section 1 Indications and Usage** was changed to:
“OXYCONTIN is an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which treatment options are inadequate.”
3. The limitations of use in **Section 1 Indications and Usage** added language on abuse.
4. The **Black Box Warning** in **Full Prescribing Information** was changed
5. **Section 5.1 Addiction, Abuse, and Misuse** had a change in language.

V. **August 25, 2015**⁹⁷

1. The indication was changed in **Section 1 Indications and Usage** to include language on prescribing for pediatric patients.
2. A new **Section 2.1 Important Dosing and Administration Instructions** was added.

VI. **December 16, 2016**⁹⁸

1. **Section 2.9 Discontinuation of OxyContin** had a change in language.
2. Withdrawal was added to **Section 6 Adverse Reactions**.

⁹⁷ *Id.*

⁹⁸ *Id.*

DETAILED REVIEW OF LABEL CHANGES

X. July 9, 2012

12. The **Boxed Warning** in the **Highlights of Prescribing Information** section was changed.

4/2010 Original Label – Boxed Warning
OxyContin contains oxycodone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (9)
7/2012 Revised Label – Boxed Warning
OxyContin contains oxycodone, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during OxyContin therapy (5.1, 9).

13. The **Boxed Warning** in the **Full Prescribing Information** section was changed.

4/2010 Original Label – Boxed Warning
OxyContin contains oxycodone which is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. (9)
OxyContin can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. (9.2)
Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction. (2.2)
7/2012 Revised Label – Boxed Warning
OxyContin[®] contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit [see Warnings and Precautions (5.1)]. Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving OxyContin for signs of misuse, abuse, and addiction during treatment [see Drug Abuse and Dependence (9)].

14. The below language on abuse was removed from **Section 2.1 Initial Dosing**.

4/2010 Original Label – Section 2.1 language removed

risk factors for abuse or addiction; including whether the patient has a previous or current substance abuse problem, a family history of substance abuse, or a history of mental illness or depression;

15. A new **Section 2.2 Titration and Maintenance of Therapy** was added.

7/2012 Revised Label – Section 2.2 language added

Individually titrate OxyContin to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OxyContin to assess the maintenance of pain control and the relative incidence of adverse reactions. During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), periodically reassess the continued need for the use of opioid analgesics.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the OxyContin dose to decrease the level of pain. Because steady-state plasma concentrations are approximated in 1 day, OxyContin dosage adjustments may be done every 1 to 2 days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid and non-opioid medication.

If signs of excessive opioid-related adverse reactions are observed, the next dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose, each time an increase is clinically indicated.

During chronic, around-the-clock opioid therapy, especially for non-cancer pain syndromes, reassess the continued need for around-the-clock opioid therapy regularly (e.g., every 6 to 12 months) as appropriate.

16. “Do not abruptly discontinue OxyContin” was added to **Section 2.4 Discontinuation of OxyContin**.

17. A new **Section 5.1 Abuse Potential** was added.

7/2012 Revised Label – Section 5.1 language added

OxyContin contains oxycodone, an opioid agonist and a Schedule II controlled substance. Oxycodone can be abused in a manner similar to other opioid agonists legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OxyContin in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of OxyContin by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death [see *Overdosage (10)*].

Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

18. A new **Section 5.12 Avoidance of Withdrawal** was added.

7/2012 Revised Label – Section 5.12 language added

Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including OxyContin. In these patients, mixed agonists/antagonists analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing OxyContin, gradually taper the dose [see *Dosage and Administration (2.4)*]. Do not abruptly discontinue OxyContin.

19. The language in **Section 9.1 Controlled Substance** was changed.

4/2010 Original Label – Section 9.1

OxyContin contains oxycodone, which is a Schedule II controlled substance with an abuse liability similar to morphine. OxyContin, like morphine and other opioids used for analgesia, can be abused and is subject to criminal diversion.

7/2012 Revised Label – Section 9.1

OxyContin contains oxycodone, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. OxyContin can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions (5.1)*].

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

20. The language in **Section 9.2** was substantially revised.

4/2010 Original Label – Section 9.2

Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances.

With parenteral abuse, the tablet excipients can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Opioid drugs are sought by people with substance use disorders (abuse or addiction, the latter of which is also called “substance dependence”) and criminals who supply them by diverting medicines out of legitimate distribution channels. OxyContin is a target for theft and diversion.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, altering or forging of prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among people with untreated substance use disorders, and criminals who divert controlled substances.

The risks of misuse and abuse should be considered when prescribing or dispensing OxyContin. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.

Compromising an extended or controlled-release delivery system will result in the uncontrolled delivery of oxycodone and pose a significant risk to the abuser that could result in overdose and death [see *Warnings and Precautions (5.1)*]. The risk of fatal overdose is further increased when oxycodone is abused concurrently with alcohol or other CNS depressants, including other opioids [see *Warnings and Precautions (5.3)*]. Abuse may occur by taking intact tablets without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation.

Drug addiction is characterized by compulsive abuse, repeated use for non-medical purposes, loss of control over intake, craving of psychic effects and continued abuse despite harm or risk of harm in medical, social, legal or occupational domains. There is a potential for drug addiction to develop following exposure to opioids, including oxycodone. Drug addiction is a treatable disease, but relapse is common.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by intentional misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin has been diverted for non-medical use.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, proper dispensing and correct storage and handling are appropriate measures that help to limit misuse and abuse of opioid drugs. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

7/2012 Revised Label – Section 9.2

Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug seeking" behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

OxyContin, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests as required by state law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to reduce abuse of opioid drugs.

Risks Specific to Abuse of OxyContin

OxyContin is for oral use only. Abuse of OxyContin poses a risk of overdose and death. This risk is increased with concurrent abuse of OxyContin with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved OxyContin enhances drug release and increases the risk of over dose and death.

Abuse may occur by taking intact tablets without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation.

With parenteral abuse, the tablet excipients can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

21. **Section 9.3 Dependence** was substantially revised.

4/2010 Original Label – Section 9.3

Physical dependence to an opioid is manifested by characteristic withdrawal signs and symptoms after abrupt discontinuation of a drug, significant dose reduction or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome in adults is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. *[See Use In Specific Populations (8.2)]*

In general, opioids should not be abruptly discontinued *[see Dosage and Administration (2.9)]*.

7/2012 Revised Label – Section 9.3

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmeferene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OxyContin should not be abruptly discontinued *[see Dosage and Administration (2.4)]*. If OxyContin is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.9)]*.

22. The language on abuse was changed in **Section 17 Patient Counseling Information**.

4/2010 Original Label – Section 17
Advise patients that OxyContin is a drug with known abuse potential. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
7/2012 Revised Label – Section 17
<u><i>Abuse Potential</i></u> Inform patients that OxyContin contains oxycodone, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share OxyContin with others and to take steps to protect OxyContin from theft or misuse.

XI. **April 16, 2013**

2. **Section 9.2 Abuse** was revised to include the below information on Abuse Deterrence Studies.

1/2013 Revised Label – Section 9.2 language added
OxyContin is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OxyContin resulting from a change in formulation, in this section, the original formulation of OxyContin, which is no longer marketed, will be referred to as “original OxyContin” and the reformulated, currently marketed product will be referred to as OxyContin.
<u><i>In Vitro Testing</i></u> <i>In vitro</i> physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OxyContin to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OxyContin relative to an immediate-release oxycodone. When subjected to an aqueous environment, OxyContin gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies

In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OxyContin 30 mg tablets, coarsely crushed OxyContin 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OxyContin, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug-liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response ('definitely would not take drug again') and 100 represents the strongest positive response ('definitely would to take drug again').

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 34% (n=10) of subjects with finely crushed OxyContin, compared with 7% (n=2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OxyContin was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 2.

Table 2. Summary of Maximum Drug Liking (E_{max}) Data Following Intranasal Administration

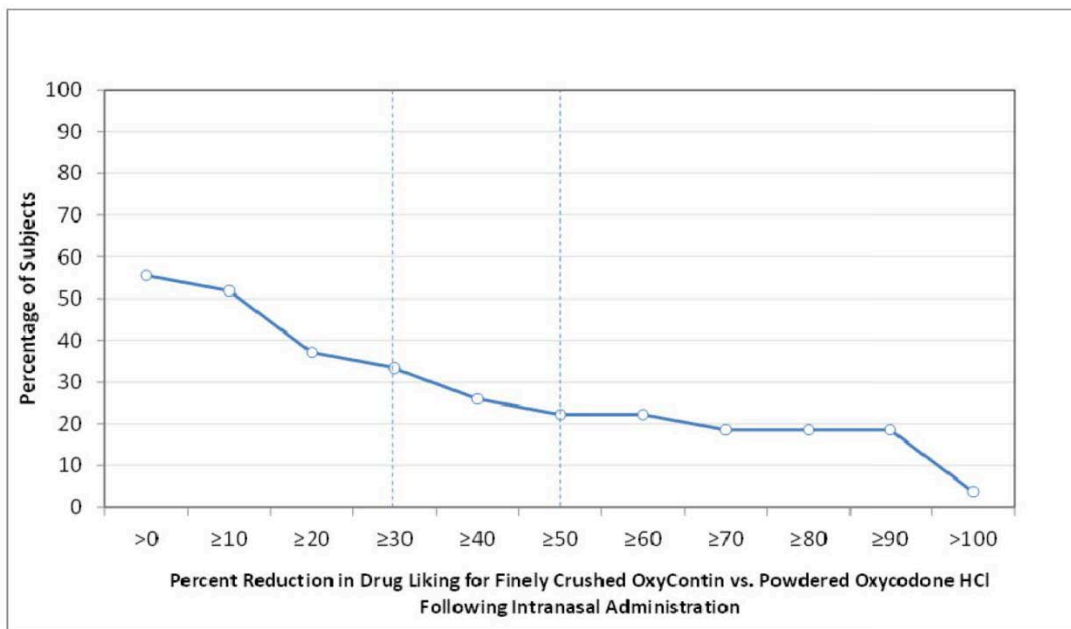
VAS Scale (100 mm)*		OxyContin (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)

	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed OxyContin compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OxyContin vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OxyContin relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OxyContin relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with OxyContin compared to oxycodone HCl, and approximately 22% (n = 6) of subjects had a reduction of at least 50% in drug liking with OxyContin compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for OxyContin vs. oxycodone HCl, N=27 Following Intranasal Administration



The results of a similar analysis of drug liking for finely crushed OxyContin relative to finely crushed original OxyContin were comparable to the results of finely crushed OxyContin relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no reduction in liking with OxyContin relative to original OxyContin. Approximately 57% (n = 16) of subjects

had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n= 8) of subjects had a reduction of at least 50% in drug liking with OxyContin compared to original OxyContin.

Summary

The *in vitro* data demonstrate that OxyContin has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that OxyContin has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OxyContin by these routes, as well as by the oral route is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OxyContin on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OxyContin contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OxyContin can be abused and is subject to misuse, addiction, and criminal diversion [See *Warnings and Precautions (5.1)* and *Drug Abuse and Dependence (9.1)*].

XII. April 16, 2014

12. The Black Box Warning in the Highlights of Prescribing Information was changed.

4/2013 Revised Label
OxyContin contains oxycodone, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during OxyContin therapy (5.1, 9).
4/2014 Revised Label
OXYCONTIN exposes users to risks of addictions, abuse and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors and conditions. (5.1)

13. The indication was changed in Section 1 Indications and Usage and the Highlights of Prescribing Information.

4/2013 Revised Label
OxyContin is an opioid agonist product indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. (1)

4/2014 Revised Label

OXYCONTIN is an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

14. The limitations of use in **Section 1 Indications and Usage** and the **Highlights of Prescribing Information** were changed to include language on abuse.

4/2014 Revised Label – Section 1 language added

Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release formulations, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)

15. The **Black Box Warning** in the **Full Prescribing Information** section was changed.

4/2013 Revised Label – Black Box Warning

OxyContin[®] contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit [see *Warnings and Precautions (5.1)*]. Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving OxyContin for signs of misuse, abuse, and addiction during treatment [see *Drug Abuse and Dependence (9)*].

4/2014 Revised Label – Black Box Warning

OXYCONTIN[®] exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OXYCONTIN and monitor all patients regularly for the development of these behaviors or conditions [see *Warnings and Precautions (5.1)*].

16. The below language was added to **Section 2.1 Initial Dosing**.

4/2014 Revised Label – Section 2.1 language added

OXYCONTIN should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

OXYCONTIN tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth [see *Patient Counseling Information (17)*]. Crushing, chewing, or dissolving OXYCONTIN tablets will result in uncontrolled delivery of oxycodone and can lead to overdose or death [see *Warnings and Precautions (5.1)*].

17. The underlined portion of the following sentence was added in **Section 2.2 Titration and Maintenance of Therapy**: “[c]ontinually reevaluate patients receiving OxyContin to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse and misuse.”

18. The below language was added to section **2.2 Titration and Maintenance of Therapy**.

4/2014 Revised Label – Section 2.2 language added

Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

Patients who experience breakthrough pain may require a dose increase of OXYCONTIN or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level

19. **Section 5.1 Addiction, Abuse, and Misuse** had a change in language.

4/2013 Revised Label – Section 5.1

OxyContin contains oxycodone, an opioid agonist and a Schedule II controlled substance. Oxycodone can be abused in a manner similar to other opioid agonists legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OxyContin in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

Assess each patient’s risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Misuse or abuse of OxyContin by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death [see *Drug Abuse and Dependence (9)* and *Overdosage (10)*].

Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

4/2014 Revised Label – Section 5.1

OXYCONTIN contains oxycodone, a Schedule II controlled substance. As an opioid, OXYCONTIN exposes users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*]. As modified-release products such as OXYCONTIN deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present [*see Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OXYCONTIN. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse or misuse prior to prescribing OXYCONTIN, and monitor all patients receiving OXYCONTIN for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as OXYCONTIN, but use in such patients necessitates intensive counseling about the risks and proper use of OXYCONTIN along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse, or misuse of OXYCONTIN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and death [*see Overdosage (10)*].

Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OXYCONTIN. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

20. "Drug abuse, addiction, and dependence" in **Section 6 Adverse Reactions** was changed to "Addiction, Abuse, and Misuse."
21. "Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances" was removed from **Section 9.2 Abuse**.
22. The language in **Section 17 Patient Counseling Information** was changed.

4/2013 Revised Label – Section 17

Inform patients that OxyContin contains oxycodone, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share OxyContin with others and to take steps to protect OxyContin from theft or misuse.

4/2014 Revised Label – Section 17

Inform patients that the use of OXYCONTIN, even when taken as recommended can result in addiction, abuse and misuse, which can lead to overdose and death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share OXYCONTIN with others and to take steps to protect OXYCONTIN from theft or misuse.

XIII. August 13, 2015

4. The indication was changed in **Section 1 Indications and Usage**.

4/2014 Revised Label – Section 1

OXYCONTIN is an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

8/2015 Revised Label – Section 1

OXYCONTIN is an opioid agonist indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

5. The below language was added to **Dosage and Administration** in the **Highlights of Prescribing Information**.

8/2015 Revised Label language added

To be prescribed only by health care providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)

6. A new **Section 2.1 Important Dosage and Administration Instructions** was added.

8/2015 Revised Label – Section 2.1 language added

OXYCONTIN should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

- Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.1)*].

XIV. **December 16, 2016**

6. The below language was added to **Section 2.1 Important Dosage and Administration Instructions** and the **Highlights of Prescribing Information**.

12/2016 Revised Label – Section 2.1 language added

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).

Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)

7. **Section 2.9 Discontinuation of OXYCONTIN** had a change in language.

8/2015 Revised Label – Section 2.9

When the patient no longer requires therapy with OXYCONTIN, gradually titrate the dosage downward to prevent signs and symptoms of withdrawal in the physically dependent patient. Do not abruptly discontinue OXYCONTIN.

12/2016 Revised Label – Section 2.9

When the patient no longer requires therapy with OXYCONTIN, taper the dosage gradually, by 25% to 50% every 2 to 4 days, while monitoring for signs and symptoms of withdrawal. If a patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OXYCONTIN *[see Warnings and Precautions (5.13), Drug Abuse and Dependence (9.3)]*.

8. Withdrawal was added to **Section 6 Adverse Reactions**.
9. **Section 9.1 Controlled Substance** was changed to “OXYCONTIN contains oxycodone, a Schedule II controlled substance.” The remaining language was moved to **Section 9.2 Abuse**.
10. “Drug abuse includes, but is not limited to, the following examples: the use of a prescription or over-the-counter drug to get ‘high’, or the use of steroids for performance enhancement and muscle build up” was removed from **Section 9.2 Abuse**.

ERRATA SHEET FOR THE 3.26.2019 EXPERT REPORT OF DAVID A. KESSLER, M.D.			
Pg. #	Parag./fn #	Now Reads	Should Read
17	24 / 14	Although the regulations [regarding fair balance, disclosure of risks, and similar matters] were promulgated in the context of prescription drug advertising, the guidance they provide on what FDA considers false or misleading in promotion has broader applicability. For example, promotional pieces that fail to present a balanced view of the risks and benefits of a product are generally considered to be false or misleading and also generally fail to reveal material facts about the product being promoted. Because both labeling pieces for prescription drugs and devices, and advertising pieces for prescription drugs and restricted devices, are considered to misbrand a product if they are false or misleading or fail to reveal material facts, drug and device manufacturers should take into account the guidance provided by these regulations when developing promotional labeling and advertising pieces for their products.	Although the regulations discussed above were promulgated in the context of prescription drug advertising, the guidance they provide on what FDA considers false or misleading in promotion has broader applicability. For example, promotional pieces that fail to present a balanced view of the risks and benefits of a product are generally considered to be false or misleading and also generally fail to reveal material facts about the product being promoted. Because both labeling pieces for prescription drugs and devices, and advertising pieces for prescription drugs and restricted devices, are considered to misbrand a product if they are false or misleading or fail to reveal material facts, drug and device manufacturers should take into account the guidance provided by these regulations when developing promotional labeling and advertising pieces for their products.
17	26 / 16	21 C.F.R. § 201.1(e)(4)(ii)(b) and (c) (2018).	21 C.F.R. § 202.1(e)(6)(i).
18	29 / 19	3/25/19 Dep. Of Scott Tomskey	3/15/19 Dep. of Scott Tomskey
29	71 / 65	<i>Id.</i>	Bloomquist, Edward. The Addiction Potential of Oxycodone (Percodan). Vol. 99, No. 2/127-130 (1963).
43	Parag. 102.1/fn 106	PKY180286806 at 11,13, 38	PKY180286806 at 13, 38
57	118.1	“In ots 1996 OxyContin launch plan ...”	“In its 1996 OxyContin launch plan ...”
60	121	<i>Purdue also created Partners Against Pain, a pain advocacy organization, to promote the claim that addiction to opioids is rare, despite lacking substantial evidence.</i>	Purdue also created Partners Against Pain, a pain advocacy organization, which promoted the claim that addiction to opioids is rare, despite lacking substantial evidence.
62	122.4	Attachment B to Plea Agreement of U.S. v. The Purdue Frederick Co. Inc., Agreed Statement of Facts, PDD1712900035 at 6.	Delete (move to para. 123)
62	123		Add as footnote: Attachment B to Plea Agreement of U.S. v. The Purdue Frederick Co. Inc., Agreed Statement of Facts, PDD1712900035 at 6.
75	146	FN 219: “... In addition, Purdue acknowledged in 2001 that ‘[t]olerance to opioids which results in a dosage increase’ was a ‘side effect’ contributing to the abuse of OxyContin and that ‘[p]atients would therefore benefit from the reduction of the development of tolerance ...’ (emphasis added).	FN 219: “... In addition, Purdue acknowledged in 2001 that ‘[t]olerance to opioids which results in a dosage increase’ was a ‘side effect’ contributing to the abuse of OxyContin and that ‘[p]atients would therefore benefit from the reduction of the development of tolerance ...’ (emphasis added). PDD9316101318 at 1.
74	Parag. 145 / Fn 217	PURCHI-00072320 at 24.	PKY18723566 at 5,6, 38
96	Parag. 167.2		Add footnote: PURCHI-000667209 at 64
99-100	Parag. 169.1/ fn 302	PPLP004032436 at 21 (emphasis added).	PPLP004032436 at 44 (emphasis added).
100	Parag. 169.6/ fn 307	PPLPMDL0030008285 (emphasis added).	PPLPMDL0080000001
100	Parag. 169.7/ fn 308	PPLPMDL0030008285 (emphasis added).	PPLPMDL0080000001

106-7	Parag. 178.3	Add footnote: PDD8013007919 at 52 and PPLPC002000136977 at 4	
107	Parag. 179/ fn 335	PDD8901580306 at 2. Purdue's REMS for OxyContin identified two primary goals: "To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of OxyContin;" and "to inform patients and healthcare professionals about the safe use of OxyContin." Risk Evaluation & Mitigation Strategy for OxyContin, PPLPC016000016240 at 1, April 1, 2010. To accomplish these goals, Purdue stated it would provide focused education and training to healthcare providers regarding the potential risk of addiction and abuse with OxyContin. <i>Id.</i> at. 2-3.	
110	Parag. 192/ fn# 347	ENDO-04908522 at 171.	
110	Parag. 190/ fn# 345	<i>Id.</i> (See http://www.endo.com/about-us/history (last visited Mar. 2, 2019).	
110	Parag. 191/ fn# 346	ENDO_DATA-OPIOID_MDL-00000001-0019	
110	Parag. 192/ fn# 347	ENDO-04908522 at 171.	
119	Parag. 200.2/ fn# 379	<i>Id.</i>	
120	Parag. 202.2/ fn# 386	ENDO-OPIOID_MDL-049271976 at 16.	
120	Parag. 204/ fn# 389	In promotion, treatment claims must generally be supported by "substantial evidence" or "two, adequate and well-controlled trials." An open-label clinical trial is insufficient to satisfy this requirement.	
129	Parag. 218.1/ fn# 427	ENDO-OR-CID-00694804 at 2	
132	Parag. 221.2/ fn# 437	<i>Id.</i> at 343:8-12, 343:16-344:2, 5-6.	
133	Parag. 221.8/ fn# 444	ENDO-OPIOID_MDL-0380727 at 3.	
152	Parag. 247.3/ fn# 505	<i>Id.</i>	
154	Parag. 248.4/ fn# 516	<i>Id.</i> at 11-17, 20-21.	
154	Parag. 248.5/ fn# 517	<i>Id.</i> at 164:24-165:1-6, 8-12.	
154	Parag. 249/ fn# 520	By 2012, Endo received reports that according to the Ohio Substance Abuse Monitoring Network "Opana was becoming popular as a replacement for OxyContin [in Akron, Cincinnati and Athens, Ohio] as it was easier to use." The report also noted that Opana 40mg tablets had eclipsed street prices for OxyContin."	
157	Parag. 254.5/ fn# 530	<i>Id.</i>	
159	Parag. 256.6/ fn# 533	No citation	
163	Parag. 262.5	<i>Id.</i> at 2- 3.	
		<i>Id.</i> at 2.	
		<i>Id.</i> at 3.	
		During the meeting, "Endo agreed to stop manufacturing of the drug product immediately and cease shipping by September 1, 2017."	
		ENDO-OR-CID-00694084	
		Larry Romaine Depo. Tr. 343:8-12, 343:16-344:2, 5-6.	
		ENDO-OPIOID_MDL-03830727 at 3.	
		ENDO-OPIOID_MDL-02314929	
		<i>Id.</i> at 162:11-17, 20-21.	
		<i>Id.</i> at 165:24-166:1-6, 8-12	
		By 2012, Endo received reports that according to Ohio's Substance Abuse Monitoring Network "Opana has become popular as a replacement for OxyContin" including in Akron, Cincinnati, and Athens, Ohio "because it is easy to use intravenously." EPI002468876.	
		EPI000832250 at 4.	
		EPI001313856 at 1.	
		<i>Id.</i> at 2.	
		<i>Id.</i> at 3.	
		During the meeting, "Endo agreed to stop manufacturing of the drug product immediately" and cease shipping by September 1, 2017.	

163	Parag. 262.5/fn# 547	Id. at 4. Weeks before the withdrawal, Endo offered wholesaler customers 20% off their purchases of the soonto-be withdrawn drug. See ENDO-OPIOID_MDL-02290107 at 1-2 (approving of Opana ER Wholesaler Promotion).	ENDO-OPIOID_MDL-01831503 at 4. Weeks before the withdrawal, Endo offered wholesaler customers 20% off their purchases of the soonto-be withdrawn drug. See ENDO-OPIOID_MDL-02290107 at 1-2 (approving of Opana ER Wholesaler Promotion).
165	269/554	A statement that Duragesic is contraindicated in the management of acute or postoperative pain was added to the contraindications section by 1998, as was a statement that Duragesic was contraindicated in “the management of mild or intermittent pain that can otherwise be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids.” (fn 554)	A statement that Duragesic is contraindicated in the management of acute or postoperative pain was added to the contraindications section by 1994, as was a statement that Duragesic was contraindicated in “the management of mild or intermittent pain that can otherwise be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids.” (fn 554)
170	285/577	<i>Id.</i> at 18.	<i>Id.</i> at 17-18.
172	290.2/588	JAN-MS-00776219 at 9-15	JAN-MS-00776219 at 5, 9-15
176	298/611	JAN-MS-00311759 at 759.	JAN-MS-00311759 at 1
177	300/613	JAN-MS-00591572 at 572.	JAN-MS-00591572 at 1
178	301/617	Janssen responded that it disagreed with DDMAC’s position but would discontinue the file card and promotional materials with the same or similar representations. JAN-MS-00238384. Janssen also agreed to send a “Dear Doctor Letter” to physicians advising them of FDA’s warning letter. See JAN-MS-00191340.	Janssen responded that it disagreed with DDMAC’s position but would discontinue the file card and promotional materials with the same or similar representations. JAN-MS-00238384. Janssen also agreed to send a “Dear Doctor Letter” to physicians advising them of FDA’s warning letter. See JAN-MS-00291340.
180	309/629	<i>Id.</i> at 5-8	<i>Id.</i> at 5-10
181	311/636	<i>Id.</i> at 4	<i>Id.</i> at 6
191	337/690	JAN-OH-000000004; JAN00118955; JAN00118956 (17 calls in 1998, 3 calls in 1999, and 20 calls in 2004). See also Schedule 12.	JAN-OH-000000004; JAN00118955; JAN00118956 (17 calls in 1998, 3 calls in 1999, and 20 calls in 2004). See also Schedule 11.
193	343/702	JAN-MS-00306718	JAN-MS-00246850
194	346/707	JAN-MS-02757583 at 588.	JAN-MS-02757583 at 6
195	349/715	JAN-MS-02338206 at 50 (PSUR for April 2000 to April 2001, showing 155 cases of abuse or addiction, including 50 which resulted in death); JAN-MS-00911743 at 13, 43 (PSUR for April 2001 to April 2002, showing 144 cases of abuse or addiction, including 20 which resulted in death); JAN00221849 at 48-49 (PSUR for April 2002 to April 2003, showing 134 cases of abuse or addiction, including 55 which resulted in death).	JAN-MS-02338206 at 50 (PSUR for April 2000 to April 2001, showing 155 cases of abuse or addiction, including 50 which resulted in death); JAN-MS-00911743 at 13, 43 (PSUR for May 2001 to April 2002, showing 144 cases of abuse or addiction, including 20 which resulted in death); JAN00221849 at 48-49 (PSUR for May 2002 to April 2003, showing 134 cases of abuse or addiction, including 55 which resulted in death).
199	362/736-737	In the period prior to the exchange above between Janssen clinical executives and the introduction of the first generic version of Duragesic in early 2005, Janssen reported over 300 annual adverse events involving abuse or addiction with the drug for April 2003 to April 2004, and over 400 for April 2004 to April 2005.	In the period prior to the exchange above between Janssen clinical executives and the introduction of the first generic version of Duragesic in early 2005, Janssen reported over 300 annual adverse events involving abuse or addiction with the drug for May 2003 to April 2004, and over 400 for May 2004 to April 2005.

200	366/743	Janssen's Duragesic system approved in the United States in 1990 was a "reservoir" patch system that "utilized a form-fill-seal design: a drug reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose that delivers fentanyl to the skin across a ratecontrolling membrane."743	Janssen's Duragesic system approved in the United States in 1990 was a "reservoir" patch system that utilized "a form-fill-seal design: a drug reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose that delivers fentanyl to the skin across a ratecontrolling membrane."743
201	369/749	JAN-MS-02119824.	JAN-MS-01139518
201	369/750	Id. at 6.	JAN-MS-01139518 at 6
202	370/751	JAN-MS-02119824	JAN-MS-01139518 at 5, 7
205	380/774	The assessment concluded that "a matrix [fentanyl patch] should not, and more likely cannot, be marketed without a strong RiskMAP that provides evidence-based elements or tools to minimize abuse and diversion and enable rapid detection of abuse and diversion that would occur."	The assessment concluded that "a matrix [fentanyl patch] should not, and more likely cannot, be marketed without a strong RiskMAP that provides evidence-based elements or tools to minimize abuse and diversion and enable rapid detection of abuse and diversion that would occur."
206	381/776	Id	JAN-MS-01196462
208	387/787-788	On November 12, 2004, Janssen, through Alza, filed a Citizen's Petition with the FDA that made the same arguments as in the white paper it commissioned. Janssen's Petition requested that the FDA take action against manufacturers of fentanyl matrix delivery systems to "reduce the potential for abuse of certain types of these products." Specifically, the Petition urged FDA to: 1) "require manufacturers of fentanyl matrix systems to develop and implement comprehensive risk minimization programs that successfully address the specific issues presented by their products" and 2) "classify matrix and reservoir fentanyl transdermal systems as different dosage forms...that are not pharmaceutical equivalents." The latter action would mean reversing FDA's decision to give Mylan's generic matrix patch an AB-rating, an action which Dr. Moskowitz had previously stated "would have a huge impact in the market," as noted above.	On November 12, 2004, Janssen, through Alza, filed a Citizen's Petition with the FDA that made the same arguments as in the white paper it commissioned. Janssen's Petition requested that the FDA take action against manufacturers of fentanyl matrix delivery systems to "reduce the potential for abuse of certain types of these products." Specifically, the Petition urged FDA to: 1) "require manufacturers of fentanyl matrix systems to develop and implement comprehensive risk minimization programs that successfully address the specific issues presented by their products" and 2) "classify matrix and reservoir fentanyl transdermal systems...as different dosage forms that are not pharmaceutical equivalents." The latter action would mean reversing FDA's decision to give Mylan's generic matrix patch an AB-rating, an action which Dr. Moskowitz had previously stated "would have a huge impact in the market," as noted above.
230	435.12/885	"Multimodal pathways that address more than one pathway may provide more comprehensive relief"	"Multimodal treatments that address more than one pathway may provide more comprehensive relief"
235	440.9/912	Id. at 54, 65	Id. at 54, 64
238	441.3/922	441.3. A "Pain Business Review" for Nucynta IR & ER dated April 23, 2014 contained a "NUCYNTA ER Positioning Statement" asserting that Nucynta "offers a superior overall clinical profile because: it provides best-in-class efficacy across multiple pain types... [and] proven GI tolerability so that: physicians and patients can achieve their individualized pain improvement goals without many of the challenges typically associated with traditional opioids."922 No evidence was cited to support these claims.	441.3. A "Pain Business Review" for Nucynta IR & ER dated April 23, 2014 contained a "NUCYNTA ER Positioning Statement" asserting that Nucynta "offers a superior overall clinical profile because: it provides best-in-class efficacy across multiple pain types... [and] proven GI tolerability... so that: physicians and patients can achieve their individualized pain improvement goals without many of the challenges typically associated with traditional opioids."922 No evidence was cited to support these claims.

239	442.2/[no fn]	no cite	JAN-MS-02273742 at 3-4
239	442.2/926	<i>Id.</i> at 2	<i>Id.</i> at 3
250	457.1/976	<i>Id.</i>	JAN-MS-03090610 at 2
267	512		ACTAVIS0238310 at 7
270	389.1	389.1	520.1
270	389.2	389.2	520.2
270	389.3	389.3	520.3
270	389.4	389.4	520.4
271	382.1	382.1	521.1
271	382.2	382.2	521.2
271	382.3	382.3	521.3
275	534.1/1090	Jennifer Altier Dep., Ex. 2 (August 2, 2018).	Jennifer Altier Dep., Ex. 2 (August 2, 2018).
275	535/1093	Jennifer Altier Dep., Ex. 2 (August 2, 2018).	Jennifer Altier Dep., Ex. 2 (August 2, 2018).
276	539/1098	MNK-T1 0001279950 at 8	MNK-T1 0001279950 at 4, 8
277	543/1102	See Exhibit 5 to Mallinckrodt's Supplemental Responses and Objections to Interrogatories Nos. 1, 5, 7, 8, 9, 16, 21, 22, 23, 27, 30, 31, 32, 33, and 35, dated January 30, 2019.	See Exhibit E to Mallinckrodt's Supplemental Responses and Objections to Interrogatories Nos. 1, 5, 7, 8, 9, 16, 21, 22, 23, 27, 30, 31, 32, 33, and 35, dated January 30, 2019.
278	546/1106	MNK-T1 0000255243 at 33-34.	MNK-T1 0000255243 at 33-35.
279	548.2/1110	MNK-T1 0000255243 at 476.	MNK-T1 0000255243 at 46-47.
280	549.3	In a 2011 Marketing Plan, Mallinckrodt's positioning statement for Exalgo focused on the benefits from its pharmacokinetic profile; stating that Exalgo "eliminates the peaks and troughs" and provides "smooth, steady hydromorphone blood levels" and "resulting in once-daily predictable chronic pain relief."	In a 2011 Marketing Plan, Mallinckrodt's positioning statement for Exalgo focused on the benefits from its pharmacokinetic profile, stating that Exalgo "eliminates the peaks and troughs" and provides "smooth, steady hydromorphone blood levels" and "resulting in once-daily predictable chronic pain relief."
285	555.2/1126	GALER, BRADLEY & C. ARGOFF., DEFEAT CHRONIC PAIN NOW! (2010) at 176-178.	GALER, BRADLEY & C. ARGOFF., DEFEAT CHRONIC PAIN NOW! (2010) at 23-25.
287	559.4/1130	MNK-T1 0001492936 at slide20.	MNK-T1 0001492936 at slide 51.
288	560/1137	MNK-T1 0001786865 at9.	MNK-T1 0001786865 at 5.
288	561/1138	MNK-T1 0007169529 at 23.	MNK-T1 0007169529 at 2-3.
289	565/1140	See Exhibit 5 to Mallinckrodt's Supplemental Responses and Objections to Interrogatories Nos. 1, 5, 7, 8, 9, 16, 21, 22, 23, 27, 30, 31, 32, 33, and 35, dated January 30, 2019.	See Exhibit E to Mallinckrodt's Supplemental Responses and Objections to Interrogatories Nos. 1, 5, 7, 8, 9, 16, 21, 22, 23, 27, 30, 31, 32, 33, and 35, dated January 30, 2019.
291	1.1	1.1	574.2
291	1.1	"Should there be a FN to MNK-T1-0000102166"	Delete
292	1.2	1.2	574.3
292	2	2	574a
292	574.1		MNK-T1 0000102169
293	574.1, paragraph 2.1		MNK-T1 0000127926
300	Parag. 591.1/ fn 1181	See SFC000000001; END000000002; JAN000000001	See SFC000000001; JAN000000001; END000000002
300	Parag. 591.2/ fn 1182	END000000002; JAN000000001	SFC000000001; JAN000000001; END000000002
300	Parag. 591.3/ fn 1183	ENDO-OPIOID MDL-06234588; JAN000000001	ENDO-OPIOID MDL-06234588
303	Parag. 598/ fn 1198	JAN-MS-00723779	JAN-MS-00409411
304	Parag. 600/ fn 1204	PPLPC0128341 at 3	PPLPC013000128341 at 3
305	Parag. 605.3/ fn 1209	JJ-SFC-000000001	JAN000000001

305	Parag. 603		PPLPC018000395220
306	Parag. 607.1/ fn 1214	Paragraph states - "Physical dependence - which is not addiction - may occur as a result of taking these medications if you stop taking these medications suddenly. This usually is not a problem if you go off your medications generally."	"Physical dependence - which is not addiction - may occur as a result of taking these medications if you stop taking these medications suddenly. This usually is not a problem if you go off your medications gradually."
308	Parag. 607.9/ fn 1222	ENDO-OPIOD MDL-00654219	ENDO-OPIOID MDL-00654219
310	Parag. 610.1/ fn 1230	FSMB 00000050 at 11-12	MDL FSMB 000000050 at 11-12.
310	Parag. 610.2/ fn 1232	FSMB 00000050 at 13	MDL FSMB 000000050
310	Parag. 610.3/ fn 1233	FSMB 00000050	MDL FSMB 000000050
310	Parag. 610.4/ fn 1234	FSMB 00000050	MDL FSMB 000000050
311	Parag. 613/ fn 1236	PPLPC002000136977 at 2.	PPLPC002000136977 at 1, 4
313	Parag. 620/ fn 1247	FSMB0000000050	MDL FSMB 000000050

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